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(54) Title: COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

(57) Abstract

Compounds and methods for treating lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment of lung cancer. The invention is more specifically related to nucleotide sequences that are preferentially expressed in lung tumor tissue, together with polypeptides encoded by such nucleotide sequences. The inventive nucleotide sequences and polypeptides may be used in vaccines and pharmaceutical compositions for the treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and methods for the therapy of lung cancer. In a first aspect, isolated polynucleotides encoding lung tumor polypeptides are provided, such polynucleotides comprising a nucleotide sequence selected

from the group consisting of: (a) sequences provided in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; (b) sequences complementary to a sequence provided in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; and (b) variants of the sequences of (a) or (b).

In a second aspect, isolated polypeptides are provided that comprise at least an immunogenic portion of a lung tumor protein or a variant thereof. In specific embodiments, such polypeptides comprise an amino acid sequence encoded by a DNA sequence comprising a nucleotide sequence selected from the group consisting of (a) sequences recited in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; (b) sequences complementary to a sequence provided in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; and (c) variants of the sequences of (a) and (b).

In related aspects, expression vectors comprising the inventive polynucleotides, together with host cells transformed or transfected with such expression vectors are provided. In preferred embodiments, the host cells are selected from the group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known lung tumor antigen, are provided.

The present invention further provides pharmaceutical compositions comprising one or more of the above polypeptides, fusion proteins or polynucleotides and a physiologically acceptable carrier, together with vaccines comprising one or more such polypeptides, fusion proteins or polynucleotides in combination with an immune response enhancer.

In related aspects, the present invention provides methods for inhibiting the development of lung cancer in a patient, comprising administering to a patient an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

In yet a further aspect of the present invention, methods are provided for detecting lung cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to a polypeptide disclosed

herein: and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of lung cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the polypeptides disclosed herein; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent: (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of lung cancer.

The present invention further provides methods for detecting lung cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide that encodes one of the polypeptides disclosed herein: and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181.

In a further aspect, the present invention provides a method for detecting lung cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide that encodes one of the polypeptides disclosed herein; and (c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181.In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

In yet a further aspect, methods for the treatment of lung cancer in a patient are provided, the methods comprising obtaining PBMC from the patient, incubating the PBMC with a polypeptide of the present invention (or a polynucleotide that encodes such a polypeptide) to provide incubated T cells and administering the incubated T cells to the patient. In present invention additionally provides methods for the treatment of lung cancer that comprise incubating antigen presenting cells with a polypeptide of the present invention (or a polynucleotide that encodes such a polypeptide) to provide incubated antigen presenting cells and administering the incubated antigen presenting cells to the patient. In certain embodiments, the antigen presenting cells are selected from the group consisting of dendritic cells and macrophages. Compositions for the treatment of lung cancer comprising T cells or antigen presenting cells that have been incubated with a polypeptide or polynucleotide of the present invention are also provided. These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons

SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons

SEQ ID NO: 3 is the determined cDNA sequence for L263C2c

SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons

SEQ ID NO: 5 is the determined cDNA sequence for L263C1b

SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons

SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons

SEQ ID NO: 8 is the determined cDNA sequence for L366C1a

SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons

SEQ ID NO: 10 is the determined cDNA sequence for L163C1c

SEQ ID NO: 11 is the determined cDNA sequence for L163C1b

SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons

SEQ ID NO: 13 is the determined cDNA sequence for L255C1b

SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons

SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons

SEQ ID NO: 16 is the determined cDNA sequence for L163C1a

SEQ ID NO: 17 is the determined cDNA sequence for LT86-1

SEQ ID NO: 18 is the determined cDNA sequence for LT86-2

SEQ ID NO: 19 is the determined cDNA sequence for LT86-3

SEQ ID NO: 20 is the determined cDNA sequence for LT86-4

SEQ ID NO: 21 is the determined cDNA sequence for LT86-5

SEQ ID NO: 22 is the determined cDNA sequence for LT86-6

SEQ ID NO: 23 is the determined cDNA sequence for LT86-7

SEQ ID NO: 24 is the determined cDNA sequence for LT86-8

SEQ ID NO: 25 is the determined cDNA sequence for LT86-9

SEQ ID NO: 26 is the determined cDNA sequence for LT86-10

SEQ ID NO: 27 is the determined cDNA sequence for LT86-11

SEQ ID NO: 28 is the determined cDNA sequence for LT86-12

SEQ ID NO: 29 is the determined cDNA sequence for LT86-13

SEQ ID NO: 30 is the determined cDNA sequence for LT86-14

SEQ ID NO: 31 is the determined cDNA sequence for LT86-15

SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1

SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2

SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3

SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4

SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5

SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6

SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7

SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8

SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9

SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10

SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11

SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12

SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13
SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14
SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15
SEQ ID NO: 47 is a $(dT)_{12}$AG primer
SEQ ID NO: 48 is a primer
SEQ ID NO: 49 is the determined 5' cDNA sequence for L86S-3
SEQ ID NO: 50 is the determined 5' cDNA sequence for L86S-12
SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16
SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25
SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36
SEQ ID NO: 54 is the determined 5' cDNA sequence for L86S-40
SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46
SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3
SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12
SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16
SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25
SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36
SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40
SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46
SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30
SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41
SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9
SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4
SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4
SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20
SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21
SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22
SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26
SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27
SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20

SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21
SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22
SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26
SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27
SEQ ID NO: 78 is the determined extended cDNA sequence for L86S-12
SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36
SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46
SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12
SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36
SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46
SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6
SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11
SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14
SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29
SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34
SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39
SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47
SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49
SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51
SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6
SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11
SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14
SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29
SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34
SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39
SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47
SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49
SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51
SEQ ID NO: 102 is the determined DNA sequence for SLT-T1
SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3
SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5
SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7
SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9
SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10
SEQ ID NO: 109 is the determined 5' cDNA sequence for SLT-T11
SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12
SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1
SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2
SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3
SEQ ID NO: 114 is the predicted amino acid sequence for SLT-T10
SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12
SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3
SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4
SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7
SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8
SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9
SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3
SEQ ID NO: 122 is the predicted amino acid sequence for SALT-T4
SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T7
SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8
SEQ ID NO: 125 is the predicted amino acid sequence for SALT-T9
SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1
SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2
SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7
SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13
SEQ ID NO: 130 is the determined cDNA sequence for PSLT-27
SEQ ID NO: 131 is the determined cDNA sequence for PSLT-28
SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30
SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40

SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69
SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71
SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73
SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79
SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03
SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09
SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011
SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041
SEQ ID NO: 142 is the determined cDNA sequence for PSLT-62
SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6
SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37
SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74
SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010
SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012
SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037
SEQ ID NO: 149 is the determined 5' cDNA sequence for SAL-3
SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24
SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25
SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33
SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50
SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57
SEQ ID NO: 155 is the determined 5' cDNA sequence for SAL-66
SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82
SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99
SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104
SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109
SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5
SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8
SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12
SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14

SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16
SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23
SEQ ID NO: 166 is the determined 5' cDNA sequence for SAL-26
SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29
SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32
SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39
SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42
SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43
SEQ ID NO: 172 is the determined 5' cDNA sequence for SAL-44
SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48
SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68
SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72
SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77
SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86
SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88
SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93
SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100
SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105
SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3
SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24
SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25
SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25
SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33
SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50
SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57
SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66
SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66
SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82
SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99
SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104

SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5
SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8
SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12
SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14
SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16
SEQ ID NO: 199 is the predicted amino acid sequence for SAL-23
SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26
SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29
SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32
SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39
SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42
SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43
SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44
SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48
SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68
SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72
SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77
SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86
SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88
SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93
SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100
SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105
SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy of lung cancer. The compositions described herein include polypeptides, fusion proteins and polynucleotides. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In one embodiment, the inventive polypeptides comprise at least a portion of a protein that is expressed at a greater level in human lung tumor tissue than in normal lung tissue. Preferably, the level of RNA encoding the polypeptide is at least 2-fold higher in tumor tissue. Such polypeptides include, but are not limited to, polypeptides (and immunogenic portions thereof) encoded by the nucleotide sequences provided in SEQ ID NO: 1-16 and variants thereof.

In a second embodiment, the inventive polypeptides comprise at least a portion of a immunogenic lung tumor protein, including but not limited to polypeptides wherein the lung tumor protein includes an amino acid sequence encoded by a polynucleotide including a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NO: 17-31, 49-55, 63,64, 66, 68-72, 78-80 and 84-92, (b) the complements of said nucleotide sequences, and (c) variants of such sequences.

In a third embodiment, the inventive polypeptides comprise at least a portion of a lung tumor protein, including polypeptides wherein the lung tumor protein includes an amino acid sequence encoded by a polynucleotide including a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NO: 102-110, 116-120 and 126-181, (b) the complements of said nucleotide sequences, and (c) variants of such sequences.

As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above lung tumor proteins may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may (but need not) be immunoreactive and/or antigenic. As detailed below, such polypeptides may be isolated from lung tumor tissue or prepared by synthetic or recombinant means.

As used herein, an "immunogenic portion" of a lung tumor protein is a portion that is capable of eliciting an immune response in a patient inflicted with lung cancer and as such binds to antibodies present within sera from a lung cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions

of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of lung cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides.

A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the antigenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide

variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA, 2*:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The lung tumor antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X

SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Resarch Foundaiton, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad., Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

The lung tumor polypeptides of the present invention, and polynucleotides encoding such polypeptides, may be isolated from lung tumor tissue using any of a variety of methods well known in the art. For example, cDNA molecules encoding polypeptides preferentially expressed in lung tumor tissue may be cloned on the basis of the lung tumor-specific expression of the corresponding mRNAs, using differential display PCR. This technique compares the amplified products from RNA templates prepared from normal lung and lung tumor tissue. cDNA may be prepared by reverse transcription of RNA using a $(dT)_{12}AG$ primer. Following amplification of the cDNA using a random primer, a band corresponding to an amplified product specific to the tumor RNA may be cut out from a silver stained gel and subcloned into a suitable vector. Examples of cDNA sequences that may be isolated using this procedure include those provided in SEQ ID NO: 1-16.

cDNA molecules encoding immunogenic lung tumor polypeptides may be prepared by screening a cDNA expression library prepared from a lung tumor sample with sera from the same patient as the tumor sample, as described in detail in Example 2 below. Examples of cDNA sequences that may be isolated using this procedure include those provided in SEQ ID NO: 17-31. Additional cDNA molecules encoding lung tumor polypeptides may be obtained by screening such a cDNA expression library with mouse anti-lung tumor serum as described below in Example 3. Examples of cDNA sequences that may thus be isolated are provided in SEQ ID NO: 49-55, 63, 64 and 126-148. cDNA sequences encoding lung tumor antigens may also be isolated by screening of lung tumor cDNA

libraries prepared from SCID mice with mouse anti-tumor sera, as described below in Example 4. Examples of cDNA sequences that may be isolated using this technique are provided in SEQ ID NO: 149-181.

A gene encoding a polypeptide described herein (or a portion thereof) may, alternatively, be amplified from human genomic DNA, or from lung tumor cDNA, via polymerase chain reaction. For this approach, sequence-specific primers may be designed based on the nucleotide sequences provided herein and may be purchased or synthesized. An amplified portion of a specific nucleotide sequence may then be used to isolate the full length gene from a human genomic DNA library or from a lung tumor cDNA library, using well known techniques, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY (1989).

Once a DNA sequence encoding a polypeptide is obtained, the polypeptide may be produced recombinantly by inserting the DNA sequence into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polynucleotide that encodes the recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as COS or CHO cells. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof. Supernatants from suitable host/vector systems which secrete the recombinant polypeptide may be first concentrated using a commercially available filter. The concentrate may then be applied to a suitable purification matrix, such as an affinity matrix or ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify the recombinant polypeptide.

Such techniques may also be used to prepare polypeptides comprising portions or variants of the native polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as

the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known lung tumor antigen, together with variants of such fusion proteins. The fusion proteins of the present invention may (but need not) include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible

extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med., 336*:86-91 (1997)).

Polypeptides that comprise an immunogenic portion of a lung tumor protein may generally be used for therapy of lung cancer, wherein the polypeptide stimulates the patient's own immune response to lung tumor cells. The present invention thus provides methods for using one or more of the compounds described herein (which may be polypeptides, polynucleotides or fusion proteins) for immunotherapy of lung cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with disease, or may be free of detectable disease. Accordingly, the compounds disclosed herein may be used to treat lung cancer or to inhibit the development of lung cancer. In a preferred embodiment, the compounds are administered

either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the inventive polypeptide is generally present within a pharmaceutical composition or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more such polypeptides and an immune response enhancer, such as an adjuvant, biodegradable microsphere (*e.g.*, polylactic galactide) or a liposome (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of lung tumor antigens, either incorporated into a fusion protein as described above (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain DNA encoding one or more of the above polypeptides and/or fusion proteins, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a lung cell antigen on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *PNAS 91*:215-219, 1994; Kass-Eisler et al., *PNAS 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of

ordinary skill in the art. The DNA may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science 259*:1745-1749, 1993, reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that is effective to raise an immune response (cellular and/or humoral) against lung tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Within certain embodiments, polynucleotides of the present invention may be formulated so as to permit entry into a cell of a mammal, preferably a human, and expression therein. Such formulations are particularly useful for therapeutic purposes. Those of skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cells, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g. avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of skill in the art. A retroviral vector may additionally transfer or incorporate a targeting moiety, such as a gene that encodes for a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods know to those of ordinary skill in the art.

Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

In passive immunotherapy, treatment involves the delivery of biologic reagents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, tumor-infiltrating lymphocytes), killer cells

(Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. These *in vitro* culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above, the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B-cells, may be pulsed with immunoreactive polypeptides or transfected with a polynucleotide sequence(s), using standard techniques well known in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term *in vivo*. Studies have demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al. *Ibid*).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. (*Crit. Rev. Oncol. Hematol.*. *22*(3), 213, 1996).

In another embodiment, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antige-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al. ("Therapy With Cultured T Cells: Principles Revisited, " *Immunological Reviews*, *157*:177, 1997 –

Additionally vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

In one embodiment, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.Polypeptides and fusion proteins of the present invention may also be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human lung tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without lung cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a lung tumor protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic lung cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic lung cancer. Suitable portions of such lung tumor proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic lung cancer in substantially all (*i. e.*,

at least about 80%, and preferably at least about 90%) of the patients for which lung cancer would be indicated using the full length protein, and that indicate the absence of lung cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human lung tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human lung tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic lung cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic lung tumors by such procedures are considered to be useful in assays for detecting primary or metastatic human lung tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human lung tumors may be used as markers for diagnosing lung cancer or for monitoring disease progression in patients. In one embodiment, lung cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera, urine and/or lung secretions.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally

be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See*, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may

be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is

then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal

that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without lung cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for lung cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for lung cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of lung cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody

sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of lung cancer. In this embodiment, assays as described above for the diagnosis of lung cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, lung cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, lung cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol. 6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation

of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate lung tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction

between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may

be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify lung tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide encoding a lung tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a lung tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a polynucleotide having a partial sequence selected from SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide having a partial sequence provided in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect lung tumor-specific sequences in biological samples, including blood, semen, lung tissue and/or lung tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC cDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from breast tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a $(dT)_{12}AG$ (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM $MgCl_2$, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

Example 2

USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some homology with a *C. elegans* leucine

aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

Example 3

USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding

predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology previously identified human polynucleotide sequences.

Example 4

USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence

tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Example 5

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 ^{0}C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor colon tumor and breast tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol.* *9*:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer* *65*:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun.* *214*:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol.* *9*:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158;

(b) the complements of sequences provided in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; and

(c) variants of the sequences of (a) and (b).

2. An isolated polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide of claim 1.

3. The isolated polypeptide of claim 2 wherein the polypeptide comprises a sequence selected from the group of sequences recited in SEQ ID NO: 182, 184-193 and 216.

4. A polynucleotide comprising a nucleotide sequence encoding the polypeptide of claim 3.

5. An expression vector comprising the polynucleotide of claims 1 or 4.

6. A host cell transformed with the expression vector of claim 5.

7. The host cell of claim 6 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.

8. A pharmaceutical composition comprising the polypeptide of claim 2 and a physiologically acceptable carrier.

9. A vaccine comprising the polypeptide of claim 2 and an immune response enhancer.

10. The vaccine of claim 9 wherein the immune response enhancer is an adjuvant.

11. A vaccine comprising the polynucleotide of claims 1 or 4 and an immune response enhancer.

12. The vaccine of claim 11 wherein the immune response enhancer is an adjuvant.

13. A pharmaceutical composition for the treatment of lung cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a lung protein or of a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181;

(b) sequences complementary to the sequences of SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181; and

(c) variants of the sequences of (a) and (b).

14. A vaccine for the treatment of lung cancer comprising a polypeptide and an immune response enhancer, said polypeptide comprising an immunogenic portion of a lung protein or of a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181;

(b) sequences complementary to the sequences of SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181; and

(c) variants of the sequences of (a) and (b).

15. A vaccine for the treatment of lung cancer comprising a polynucleotide and an immune response enhancer, the polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181;

(b) sequences complementary to the sequences of SEQ ID NO: 12-18, 20, 21, 26, 49, 50, 52, 54, 64, 66, 68, 69, 71, 78, 84, 85, 88, 91, 92, 116-120, 126-138, 140-142, 150, 155 and 159-181; and

(c) variants of the sequences of (a) and (b).

16. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claims 8 or 13.

17. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of any one of claims 9, 11, 14 or 15.

18. A fusion protein comprising at least one polypeptide according to claim 2.

19. A fusion protein comprising at least two polypeptides according to claim 2.

20. A fusion protein comprising a polypeptide according to claim 2 and a known lung tumor antigen.

21. A pharmaceutical composition comprising a fusion protein according to any one of claims 18-20 and a physiologically acceptable carrier.

22. A vaccine comprising a fusion protein according to any one of claims 18-20 and an immune response enhancer.

23. The vaccine of claim 22 wherein the immune response enhancer is an adjuvant.

24. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claim 21.

25. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of claim 22.

26. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient a polynucleotide under conditions such that the polynucleotide enters a cell of the patient and is expressed therein, the polynucleotide having a sequence selected from the group consisting of:

(a) a sequence provided in SEQ ID NO: 102;

(b) sequences complementary to a sequence of SEQ ID NO: 102; and

(c) variants of the sequence of SEQ ID NO: 102.

27. A method for detecting lung cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-31, 49-

55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof; and

(b) detecting in the sample a polypeptide that binds to the binding agent, thereby detecting lung cancer in the patient.

28. The method of claim 27 wherein the binding agent is a monoclonal antibody.

29. The method of claim 28 wherein the binding agent is a polyclonal antibody.

30. A method for monitoring the progression of lung cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof;

(b) determining in the sample an amount of a polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of lung cancer in the patient.

31. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158;

(b) the complements of nucleotide sequences recited in SEQ ID NO: 1-11, 19, 22-25, 27-31, 51, 53, 55, 63, 70, 72, 79, 80, 86, 87, 89, 90, 102-107, 109, 139, 143-149, 151-154 and 156-158; and

(c) variants of the sequences of (a) and (b).

32. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient a therapeutically effective amount of a monoclonal antibody according to claim 31.

33. The method of claim 32 wherein the monoclonal antibody is conjugated to a therapeutic agent.

34. A method for detecting lung cancer in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof; and

(c) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting lung cancer.

35. The method of claim 34, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181.

36. A diagnostic kit comprising:

(a) one or more monoclonal antibodies according to claim 31; and

(b) a detection reagent.

37. The kit of claim 36 wherein the monoclonal antibody is immobilized on a solid support.

38. The kit of claim 37 wherein the solid support comprises nitrocellulose, latex or a plastic material.

39. The kit of claim 36 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

40. The kit of claim 39 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

41. The kit of claim 39 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

42. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof.

43. The diagnostic kit of claim 42 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences

provided in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof.

44. A method for detecting lung cancer in a patient, comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said nucleotide sequences and variants thereof; and

(c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting lung cancer in the patient.

45. The method of claim 44 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said nucleotide sequences and variants thereof.

46. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120 and 126-181, the complements of said sequences and variants thereof.

47. The diagnostic kit of claim 46, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 1-31, 49-55,

63, 64, 66, 68-72, 78-80, 84-92 and 102-110, the complements of said sequences and variants thereof.

48. A method for treating lung cancer in a patient, comprising the steps of:
(a) obtaining peripheral blood cells from the patient;
(b) incubating the cells in the presence of at least one polypeptide of claim 2, such that T cells proliferate; and
(c) administering the proliferated T cells to the patient.

49. A method for treating lung cancer in a patient, comprising the steps of:
(a) obtaining peripheral blood cells from the patient;
(b) incubating the cells in the presence of at least one polynucleotide of claim 1, such that T cells proliferate; and
(c) administering to the patient the proliferated T cells.

50. The method of any one of claims 48 and 49 wherein the step of incubating the T cells is repeated one or more times.

51. The method of any one of claims 48 and 49 wherein step (a) further comprises separating T cells from the peripheral blood cells, and the cells incubated in step (b) are the T cells.

52. The method of any one of claims 48 and 49 wherein step (a) further comprises separating CD4+ cells or CD8+ cells from the peripheral blood cells, and the cells proliferated in step (b) are CD4+ or CD8+ T cells.

53. The method of any one of claims 48 and 49 wherein step (b) further comprises cloning one or more T cells that proliferated in the presence of the polypeptide.

54. A composition for the treatment of lung cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of claim 2, in combination with a

pharmaceutically acceptable carrier.

55. A composition for the treatment of lung cancer in a patient, comprising T cells proliferated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.

56. A method for treating lung cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polypeptide of claim 2; and

(b) administering to the patient the incubated antigen presenting cells.

57. A method for treating lung cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polynucleotide of claim 1; and

(b) administering to the patient the incubated antigen presenting cells.

58. The method of claims 54 or 55 wherein the antigen presenting cells are selected from the group consisting of dendritic cells and macrophage cells.

59. A composition for the treatment of lung cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of claim 2, in combination with a pharmaceutically acceptable carrier.

60. A composition for the treatment of lung cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.

SEQUENCE LISTING

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<210> 14
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<213> Homo sapiens

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<212> DNA
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<211> 522
<212> DNA
<213> Homo sapiens

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<211> 317
<212> DNA
<213> Homo sapiens

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aaaaaaaaaa actcgag 317

<210> 18
<211> 392
<212> DNA
<213> Homo sapiens

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cggacatccc agagaagccc caagaccccc cg 392

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<211> 2624
<212> DNA
<213> Homo sapiens

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<211> 488
<212> DNA
<213> Homo sapiens

<400> 20
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<210> 21
<211> 391
<212> DNA
<213> Homo sapiens

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<210> 22
<211> 1320
<212> DNA
<213> Homo sapiens

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<210> 23
<211> 633
<212> DNA
<213> Homo sapiens

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<210> 24
<211> 1328
<212> DNA
<213> Homo sapiens

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<211> 1758
<212> DNA
<213> Homo sapiens

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<210> 26
<211> 493
<212> DNA
<213> Homo sapiens

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<210> 27
<211> 1331
<212> DNA
<213> Homo sapiens

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<210> 28
<211> 1333
<212> DNA
<213> Homo sapiens

<400> 28
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agatggttgg aatcgagtac atcctttttgc atgctcaaga gcccattctt ttcatcattc 240
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ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg 360
cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt 420
ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 480
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 540
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 600
ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 660

agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 780
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<210> 29
<211> 813
<212> DNA
<213> Homo sapiens

<400> 29
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<210> 30
<211> 1316
<212> DNA
<213> Homo sapiens

<400> 30
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gtggagtcaa atatactttt caccatcagg aaatatagtt gctcatgaaa actgtttgct 180
gtattcatca ggactggtgg agtgtgagac tcttgatcta cgtaatacaa ttagaaactt 240
tgatgtcaaa tctgtaaaga aagagatctg gagaggaaga agattgaaat gctcattctg 300
taacaaagga ggcgccaccg tggggtgtga tttatggttc tgtaagaaga gttaccacta 360
tgtctgtgcc aaaaaggacc aagcaattct tcaagttgat ggaaaccatg gaacttacaa 420
attattttgc ccagaacatt ctccagaaca agaagaggcc actgaaagtg ctgatgaccc 480
aagcatgaag aagaagagag gaaaaaacaa acgcctctca tcaggccctc ctgcacagcc 540
aaaaacgatg aaatgtagta acgccaaaag acatatgaca gaagagcctc atggtcacac 600
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actatttgaa cacatactag aaaatatgga ttcagttcat ggaagacttg tggatgagac 720
tgcctcagag tcggactatg aagggatcga gaccttactg tttgactgtg gattatttaa 780
agacacacta agaaaattcc aagaagtaat caagagtaaa gcttgtgaat gggaagaaag 840
gcaaaggcag atgaagcagc agcttgaggc acttgcagac ttacaacaaa gcttgtgctc 900

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<210> 31
<211> 1355
<212> DNA
<213> Homo sapiens

<400> 31
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acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 180
agatggttgg aatcgagtac atcctttttgc atgctcaaga gcccattctt ttcatcattc 240
ggaagcaaca gcggcagtcc cctgcccaag ttatcccact agctgattac tatatcattg 300
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ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 480
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<210> 32
<211> 80
<212> PRT
<213> Homo sapiens

<400> 32
Val Ser Arg Ile Arg Gly Gly Ala Lys Lys Arg Lys Lys Lys Ser Tyr
1 5 10 15

Thr Thr Pro Lys Lys Asp Lys His Gln Arg Lys Lys Val Gln Pro Ala
20 25 30

Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly Lys Ile Ser Cys Leu
35 40 45

Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala Gly Val Phe Met Ala
50 55 60

Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys Cys Leu Thr His Cys
65 70 75 80

<210> 33
<211> 130
<212> PRT
<213> Homo sapiens

<400> 33
Glu Ile Ser Asn Glu Val Arg Lys Phe Arg Thr Leu Thr Glu Leu Ile
1 5 10 15

Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
20 25 30

Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
35 40 45

Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
50 55 60

Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
65 70 75 80

Pro Glu Lys Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
85 90 95

Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
100 105 110

Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp
115 120 125

Pro Pro
130

<210> 34
<211> 506
<212> PRT
<213> Homo sapiens

<400> 34
Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
1 5 10 15

Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
20 25 30

Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro

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        35                  40                  45

Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
    50                  55                  60

Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
65                  70                  75                  80

Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
                85                  90                  95

Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
            100                 105                 110

Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
        115                 120                 125

His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
    130                 135                 140

Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
145                 150                 155                 160

Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
                165                 170                 175

Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
            180                 185                 190

Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
        195                 200                 205

Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
    210                 215                 220

Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
225                 230                 235                 240

Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
                245                 250                 255

Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
            260                 265                 270

Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
        275                 280                 285

His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
    290                 295                 300

Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
305                 310                 315                 320

His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
                325                 330                 335
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Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
340 345 350

Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
355 360 365

Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
370 375 380

Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
385 390 395 400

Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
405 410 415

Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
420 425 430

Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
435 440 445

Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
450 455 460

Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
465 470 475 480

Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys
485 490 495

Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
500 505

<210> 35
<211> 96
<212> PRT
<213> Homo sapiens

<400> 35
Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
1 5 10 15

Arg Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
20 25 30

Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Gln Phe Lys Thr
35 40 45

Thr Gln Thr His Met Asp Arg Glu Lys Val Ala Leu Lys Asp Phe Ser
50 55 60

Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65 70 75 80

Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Thr Gln Glu His Val
85 90 95

<210> 36
<211> 129
<212> PRT
<213> Homo sapiens

<400> 36
Gly Ile Val Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu
1 5 10 15

Lys Lys Ala Val Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr
20 25 30

Val Leu Trp Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn
35 40 45

Thr Ile Leu Val Gln Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro
50 55 60

Met Thr Arg Ala Phe Ile Thr His Ala Ser Ser His Gly Val Asn Glu
65 70 75 80

Ser Ile Cys Asn Gly Val Pro Met Val Met Ile Pro Leu Phe Gly Asp
85 90 95

Gln Met Asp Asn Ala Lys Arg Arg Glu Thr Lys Gly Ala Gly Val Thr
100 105 110

Leu Asn Val Leu Glu Met Thr Ser Glu Asp Leu Glu Asp Ala Leu Lys
115 120 125

Ser

<210> 37
<211> 238
<212> PRT
<213> Homo sapiens

<400> 37
Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu
1 5 10 15

Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe
20 25 30

Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr
35 40 45

Leu Glu His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His
50 55 60

Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser
65 70 75 80

Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val
85 90 95

Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu
100 105 110

Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr
115 120 125

Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His
130 135 140

Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro
145 150 155 160

Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu
165 170 175

Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu Lys Pro Gly Glu Lys
180 185 190

Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala Glu Pro Ile Pro Glu
195 200 205

Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys Asn Val Gln Gln Thr
210 215 220

Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met Arg Leu Gln
225 230 235

<210> 38
<211> 202
<212> PRT
<213> Homo sapiens

<400> 38
Lys Gly Ser Glu Gly Glu Asn Pro Leu Thr Val Pro Gly Arg Glu Lys
1 5 10 15

Glu Gly Met Leu Met Gly Val Lys Pro Gly Glu Asp Ala Ser Gly Pro
20 25 30

Ala Glu Asp Leu Val Arg Arg Ser Glu Lys Asp Thr Ala Ala Val Val
35 40 45

Ser Arg Gln Gly Ser Ser Leu Asn Leu Phe Glu Asp Val Gln Ile Thr
50 55 60

Glu Pro Glu Ala Glu Pro Glu Ser Lys Ser Glu Pro Arg Pro Pro Ile
65 70 75 80

Ser Ser Pro Arg Ala Pro Gln Thr Arg Ala Val Lys Pro Arg Leu His
85 90 95

Pro Val Lys Pro Met Asn Ala Thr Ala Thr Lys Val Ala Asn Cys Ser
100 105 110

Leu Gly Thr Ala Thr Ile Ile Gly Glu Asn Leu Asn Asn Glu Val Met
115 120 125

Met Lys Lys Tyr Ser Pro Ser Asp Pro Ala Phe Ala Tyr Ala Gln Leu
130 135 140

Thr His Asp Glu Leu Ile Gln Leu Val Leu Lys Gln Lys Glu Thr Ile
145 150 155 160

Ser Lys Lys Glu Phe Gln Val Arg Glu Leu Glu Asp Tyr Ile Asp Asn
165 170 175

Leu Leu Val Arg Val Met Glu Glu Thr Pro Asn Ile Leu Arg Ile Pro
180 185 190

Thr Gln Val Gly Lys Lys Ala Gly Lys Met
195 200

<210> 39
<211> 243
<212> PRT
<213> Homo sapiens

<400> 39
Val Asn Ala Leu Gly Ile Met Ala Ala Val Asp Ile Arg Asp Asn Leu
1 5 10 15

Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser
20 25 30

Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe Tyr Asp
35 40 45

Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr Leu Glu
50 55 60

His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln
65 70 75 80

Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala
85 90 95

Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr
100 105 110

Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala
115 120 125

Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr Cys Arg
130 135 140

Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His Glu Glu
145 150 155 160

Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro Ser Ser
165 170 175

Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu Arg Gln
180 185 190

Lys Ile Ser Thr Gln Ile Cys Ala Val Asp Gln Thr Lys Lys Glu Ala
195 200 205

Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
210 215 220

Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225 230 235 240

Arg Leu Gln

<210> 40
<211> 245
<212> PRT
<213> Homo sapiens

<400> 40
Ala Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp
1 5 10 15

Ser Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe
20 25 30

Ser Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val
35 40 45

Val Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly
50 55 60

Ile Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile
65 70 75 80

Arg Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp
85 90 95

Tyr Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser
100 105 110

Val Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala
115 120 125

Phe Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr
130 135 140

Trp Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys
145 150 155 160

Ala Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val
165 170 175

Asp Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val
180 185 190

Gln Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys
195 200 205

Glu Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr
210 215 220

Thr Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys
225 230 235 240

Arg Met Arg Leu Gln
245

<210> 41
<211> 163
<212> PRT
<213> Homo sapiens

<400> 41
Gly Glu Arg Gln Gly Leu Val Ala Arg Ala Arg Leu Ser Leu Arg Pro
1 5 10 15

Ser Ile Pro Glu Leu Ser Glu Arg Thr Ser Arg Pro Cys Arg Ala Ser
20 25 30

Pro Ala Ser Leu Pro Ser Gln His Thr Ser Ser Pro Ala Gln Ala Arg
35 40 45

Val Arg Asn Leu Ala Gln Ser Thr Phe Pro Leu Ala Ala Gln Glu Thr
50 55 60

Pro Gly Arg Ala Pro Ala His Ala Pro Leu Ser Ser Phe Val Pro Gly
65 70 75 80

Val Gly Gly Arg Ser Pro Ala Ser Val Gly Ile Ser Ala Pro Gly Gly
85 90 95

Gly Pro Ser Gly Ala Ala Ala Lys Ile Pro Leu Glu Leu Thr Gln Ser
100 105 110

Arg Val Gln Lys Ile Trp Val Pro Val Asp His Arg Pro Ser Leu Pro
115 120 125

Arg Ser Cys Gly Pro Lys Leu Thr Asn Ser Pro Ala Val Phe Val Met

130 135 140

Val Gly Leu Pro Arg Pro Gly Gln Asp Leu Leu Leu His Glu Ser Leu
145 150 155 160

Leu Ala Ala

<210> 42
<211> 243
<212> PRT
<213> Homo sapiens

<400> 42
Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser
1 5 10 15

Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu
20 25 30

Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys
35 40 45

Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile Glu
50 55 60

Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys
65 70 75 80

Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr
85 90 95

Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile
100 105 110

Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp
115 120 125

Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp
130 135 140

His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys
145 150 155 160

Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala
165 170 175

Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu
180 185 190

Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala
195 200 205

Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
210 215 220

Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225 230 235 240

Arg Leu Gln

<210> 43
<211> 244
<212> PRT
<213> Homo sapiens

<400> 43
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
1 5 10 15

Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
20 25 30

Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val
35 40 45

Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile
50 55 60

Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg
65 70 75 80

Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr
85 90 95

Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val
100 105 110

Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe
115 120 125

Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp
130 135 140

Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala
145 150 155 160

Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp
165 170 175

Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln
180 185 190

Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu
195 200 205

Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr
210 215 220

Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg
225 230 235 240

Met Arg Leu Gln

<210> 44
<211> 109
<212> PRT
<213> Homo sapiens

<400> 44
Glu Leu His Phe Ser Glu Phe Thr Ser Ala Val Ala Asp Met Lys Asn
1 5 10 15

Ser Val Ala Asp Arg Asp Asn Ser Pro Ser Ser Cys Ala Gly Leu Phe
20 25 30

Ile Ala Ser His Ile Gly Phe Asp Trp Pro Gly Val Trp Val His Leu
35 40 45

Asp Ile Ala Ala Pro Val His Ala Gly Glu Arg Ala Thr Gly Phe Gly
50 55 60

Val Ala Leu Leu Leu Ala Leu Phe Gly Arg Ala Ser Glu Asp Pro Leu
65 70 75 80

Leu Asn Leu Val Ser Pro Leu Asp Cys Glu Val Asp Ala Gln Glu Gly
85 90 95

Asp Asn Met Gly Arg Asp Ser Lys Arg Arg Arg Leu Val
100 105

<210> 45
<211> 324
<212> PRT
<213> Homo sapiens

<400> 45
Arg Arg Pro Val Met Ala Gln Glu Thr Ala Pro Pro Cys Gly Pro Val
1 5 10 15

Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
20 25 30

Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
35 40 45

Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
50 55 60

Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
65 70 75 80

Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
85 90 95

Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
100 105 110

Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
115 120 125

Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro
130 135 140

Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
145 150 155 160

Ser Met Lys Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
165 170 175

Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
180 185 190

Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
195 200 205

Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
210 215 220

Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
225 230 235 240

Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys
245 250 255

Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser
260 265 270

Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu
275 280 285

Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asn
290 295 300

Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro
305 310 315 320

Glu Asp His Gln

<210> 46
<211> 244
<212> PRT
<213> Homo sapiens

<400> 46
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser

1 5 10 15

Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
20 25 30

Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val
35 40 45

Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile
50 55 60

Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg
65 70 75 80

Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr
85 90 95

Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val
100 105 110

Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe
115 120 125

Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp
130 135 140

Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala
145 150 155 160

Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp
165 170 175

Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln
180 185 190

Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu
195 200 205

Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr
210 215 220

Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg
225 230 235 240

Met Arg Leu Gln

<210> 47
<211> 14
<212> DNA
<213> Homo sapiens

<400> 47
tttttttttt ttag 14

<210> 48
<211> 10
<212> DNA
<213> Homo sapiens

<400> 48
cttcaacctc 10

<210> 49
<211> 496
<212> DNA
<213> Homo sapiens

<400> 49
gcaccatgta ccgagcactt cggctcctcg cgcgctcgcg tcccctcgtg cgggctccag 60
ccgcagcctt agcttcggct cccggcttgg gtggcgcggc cgtgccctcg_ttttggcctc 120
cgaacgcggc tcgaatggca agccaaaatt ccttccggat agaatatgat acctttggtg 180
aactaaaggt gccaaatgat aagtattatg gcgcccagac cgtgagatct acgatgaact 240
ttaagattgg aggtgtgaca gaacgcatgc caaccccagt tattaaagct tttggcatct 300
tgaagcgagc ggccgctgaa gtaaaccagg attatggtct tgatccaaag attgctaatg 360
caataatgaa ggcagcagat gaggtagctg aaggtaaatt aaatgatcat ttcctctcg 420
tggtatggca gactggatca ggaactcaga caaatatgaa tgtaaatgaa gtcattagcc 480
aatagagcaa ttgaaa 496

<210> 50
<211> 499
<212> DNA
<213> Homo sapiens

<400> 50
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 60
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggcg aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagt 499

<210> 51
<211> 887
<212> DNA
<213> Homo sapiens

<400> 51
gagtctgagc agaaaggaaa agcagccttg gcagccacgt tagaggaata caaagccaca 60
gtggccagtg accagataga gatgaatcgc ctgaaggctc agctggagaa tgaaaagcag 120
aaagtggcag agctgtattc tatccataac tctggagaca aatctgatat tcaggacctc 180
ctggagagtg tcaggctgga caaagaaaaa gcagagactt tggctagtag cttgcaggaa 240
gatctggctc atacccgaaa tgatgccaat cgattacagg atgccattgc taaggtagag 300
gatgaatacc gagccttcca agaagaagct aagaaacaaa ttgaagattt gaatatgacg 360
ttagaaaaat taagatcaga cctggatgaa aaagaaacag aaaggagtga catgaaagaa 420
accatctttg aacttgaaga tgaagtagaa caacatcgtg ctgtgaaact tcatgacaac 480
ctcattattt ctgatctaga gaatacagtt aaaaaactcc aggaccaaaa gcacgacatg 540

gaaagagaaa taaagacact ccacagaaga cttcgggaag aatctgcgga atggcggcag 600
tttcaggctg atctccagac tgcagtagtc attgcaaatg acattaaatc tgaagcccaa 660
gaggagattg gtgatctaaa gcgccggtta catgaggctc aagaaaaaaa tgagaaactc 720
acaaaagaat tggaggaaat aaagtcacgc aagcaagagg aggagcgagg cgggtataca 780
attacatgaa tgccgttgag agagatttgg cagccttaag gcagggaatg ggactgagta 840
gaaggtcctc gacttcctca gaggcaactc ctacagtaaa aaccctc 887

<210> 52
<211> 491
<212> DNA
<213> Homo sapiens

<400> 52
ggcacgagct tttccaaaaa tcatgctgct cctttctcta aagttcttac attttataga 60
aaggaacctt tcactcttga ggcctactac agctctcctc aggatttgcc ctatccagat 120
cctgctatag ctcagttttc agttcagaaa gtcactcctc agtctgatgg ctccagttca 180
aaagtgaaag tcaaagttcg agtaaatgtc catggcattt tcagtgtgtc cagtgcatct 240
ttagtggagg ttcacaagtc tgaggaaaat gaggagccaa tggaaacaga tcagaatgca 300
aaggaggaag agaagatgca agtggaccag gaggaaccac atgttgaaga gcaacagcag 360
cagacaccag gcagaaaata aggcagagtc tgaagaaatg gagacctctc aagctggatc 420
caaggataaa aagatggacc aaccacccca agccaagaag gcaaaagtga agaccagtac 480
tgtggacctg g 491

<210> 53
<211> 787
<212> DNA
<213> Homo sapiens

<400> 53
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttactttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aaccccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaac 787

<210> 54
<211> 386
<212> DNA
<213> Homo sapiens

<400> 54
ggcattttca gtgtgtccag tgcatcttta gtggaggttc acaagtctga ggaaaatgag 60
gagccaatgg aaacagatca gaatgcaaag gaggaagaga agatgcaagt ggaccaggag 120
gaaccacatg ttgaagagca acagcagcag acaccagcag aaaataaggc agagtctgaa 180
gaaatggaga cctctcaagc tggatccaag gataaaaaga tggaccaacc accccaagcc 240
aagaaggcaa aagtgaagac cagtactgtg gacctgccaa tcgagaatca gctattatgg 300

cagatagaca gagagatgct caacttgtac attgaaaatg agggtaagat gatcatgcag 360
gataaactgg agaaggagcg gaatga 386

<210> 55
<211> 1462
<212> DNA
<213> Homo sapiens

<400> 55
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttactttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaacatt tcctaaacta agaatgagag taagaaatat tttaattcat aacaattata 840
aatctgcaac tcatgaaaat gacattgcac ttgtgagact tgagaacagt gtcaccttta 900
ccaaagatat ccatagtgtg tgtctcccag ctgctaccca gaatattcca cctggctcta 960
ctgcttatgt aacaggatgg ggcgctcaag aatatgctgg ccacacagtt ccagagctaa 1020
ggcaaggaca ggtcagaata ataagtaatg atgtatgtaa tgcaccacat agttataatg 1080
gagccatctt gtctggaatg ctgtgtgctg gagtacctca aggtggagtg gacgcatgtc 1140
agggtgactc tggtggccca ctagtacaag aagactcacg gcggctttgg tttattgtgg 1200
ggatagtaag ctggggagat cagtgtggcc tgccggataa gccaggagtg tatactcgag 1260
tgacagcata cattgactgg attaggcaac aaactgggat ctagtgcaac aagtgcatcc 1320
ctgttgcaaa gtctgtatgc aggtgtgcct gtcttaaatt ccaaagcttt acatttcaac 1380
tgaaaaagaa actagaaatg tcctaattta acatcttgtt acataaatat ggtttaacaa 1440
aaaaaaaaaa aaaaaactcg ag 1462

<210> 56
<211> 159
<212> PRT
<213> Homo sapiens

<400> 56
Thr Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val
1 5 10 15

Arg Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala
20 25 30

Ala Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met Ala Ser Gln
35 40 45

Asn Ser Phe Arg Ile Glu Tyr Asp Thr Phe Gly Glu Leu Lys Val Pro
50 55 60

Asn Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe
65 70 75 80

Lys Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala
85 90 95

Phe Gly Ile Leu Lys Arg Ala Ala Ala Glu Val Asn Gln Asp Tyr Gly
100 105 110

Leu Asp Pro Lys Ile Ala Asn Ala Ile Met Lys Ala Ala Asp Glu Val
115 120 125

Ala Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr
130 135 140

Gly Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser
145 150 155

<210> 57
<211> 165
<212> PRT
<213> Homo sapiens

<400> 57
Lys Lys Ser Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met
1 5 10 15

Gly Thr Ala Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu
20 25 30

Gln Lys Gln Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys
35 40 45

Thr Lys Glu Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr
50 55 60

Asp Asp His Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile
65 70 75 80

Val Gly His Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val
85 90 95

Thr Thr Val Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln
100 105 110

Cys Arg Glu Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile
115 120 125

Arg Ser Asp Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg
130 135 140

Phe Thr Cys Lys Gly Glu Pro Val His His Phe Met Asn Thr Ser Thr
145 150 155 160

Phe Thr Glu Tyr Thr
165

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<210> 58
<211> 259
<212> PRT
<213> Homo sapiens

<400> 58
Glu Ser Glu Gln Lys Gly Lys Ala Ala Leu Ala Ala Thr Leu Glu Glu
 1               5                   10                  15

Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
             20                  25                  30

Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
         35                  40                  45

His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
     50                  55                  60

Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
 65                  70                  75                  80

Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
                 85                  90                  95

Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
            100                 105                 110

Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
        115                 120                 125

Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
    130                 135                 140

Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
145                 150                 155                 160

Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
                165                 170                 175

Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
            180                 185                 190

Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
        195                 200                 205

Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
    210                 215                 220

Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
225                 230                 235                 240

Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
                245                 250                 255
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Gly Gly Tyr

<210> 59
<211> 125
<212> PRT
<213> Homo sapiens

<400> 59
Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
1 5 10 15

Thr Phe Tyr Arg Lys Glu Pro Phe Thr Leu Glu Ala Tyr Tyr Ser Ser
20 25 30

Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
35 40 45

Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
50 55 60

Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
65 70 75 80

Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
85 90 95

Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
100 105 110

Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
115 120 125

<210> 60
<211> 246
<212> PRT
<213> Homo sapiens

<400> 60
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15

Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30

Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45

Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60

Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80

Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95

Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110

Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125

Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140

Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160

Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175

Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190

Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205

Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220

Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240

Thr Ser Gly Ile Ser Thr
245

<210> 61
<211> 128
<212> PRT
<213> Homo sapiens

<400> 61
Gly Ile Phe Ser Val Ser Ser Ala Ser Leu Val Glu Val His Lys Ser
1 5 10 15

Glu Glu Asn Glu Glu Pro Met Glu Thr Asp Gln Asn Ala Lys Glu Glu
20 25 30

Glu Lys Met Gln Val Asp Gln Glu Glu Pro His Val Glu Glu Gln Gln
35 40 45

Gln Gln Thr Pro Ala Glu Asn Lys Ala Glu Ser Glu Glu Met Glu Thr
50 55 60

Ser Gln Ala Gly Ser Lys Asp Lys Lys Met Asp Gln Pro Pro Gln Ala
65 70 75 80

Lys Lys Ala Lys Val Lys Thr Ser Thr Val Asp Leu Pro Ile Glu Asn

85 90 95

Gln Leu Leu Trp Gln Ile Asp Arg Glu Met Leu Asn Leu Tyr Ile Glu
100 105 110

Asn Glu Gly Lys Met Ile Met Gln Asp Lys Leu Glu Lys Glu Arg Asn
115 120 125

<210> 62
<211> 418
<212> PRT
<213> Homo sapiens

<400> 62
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15

Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30

Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45

Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60

Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80

Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95

Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110

Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125

Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140

Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160

Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175

Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190

Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205

Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr

210 215 220

Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240

Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255

Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270

Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285

His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300

Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305 310 315 320

Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
325 330 335

Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
340 345 350

Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
355 360 365

Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
370 375 380

Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385 390 395 400

Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
405 410 415

Gly Ile

<210> 63
<211> 776
<212> DNA
<213> Homo sapiens

<400> 63
cacagatggt gatagaggaa tccatcttgc agtcagataa agccctcact gatagagaga 60
aggcagtagc agtggatcgg gccaagaagg aggcagctga gaaggaacag gaacttttaa 120
aacagaaatt acaggagcag ccagcaacag atggaggctc aagataagag tcgcaaggaa 180
aactagccaa ctgaaggaga agctgcagat ggagagagaa cacctactga gagagcagat 240
tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa 300
gaagtatgag gagatgaatg cagagataag tcaatttaaa cgtatgattg atactacaaa 360
aaatgatgat actccctgga ttgcacgaac cttggacaac cttgccgatg agctaactgc 420
aatattgtct gctcctgcta aattaattgg tcatggtgtc aaaggtgtga gctcactctt 480

taaaaagcat aagctcccct tttaaggata ttatagattg tacatatatg ctttggacta 540
tttttgatct gtatgttttt cattttcatt cagcaagttt tttttttttt tcagagtctt 600
actctgttgc ccaggctgga gtacagtggt gcaatctcag ctcactgcaa cctctgcctc 660
ctgggttcaa gagattcacc tgcctcagcc ccctagtagc tgggattata ggtgtacacc 720
accacaccca gctaattttt gtattttttag tagagatggg gtttcactat gttggc 776

<210> 64
<211> 160
<212> DNA
<213> Homo sapiens

<400> 64
gcagcgctct cggttgcagt acccactgga aggacttagg cgctcgcgtg gacaccgcaa 60
gcccctcagt agcctcggcc caagaggcct gctttccact cgctagcccc gccgggggtc 120
cgtgtcctgt ctcggtggcc ggacccgggc ccgagcccga 160

<210> 65
<211> 72
<212> PRT
<213> Homo sapiens

<400> 65
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
1 5 10 15

Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val
20 25 30

Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly
35 40 45

Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile
50 55 60

Ala Ala Val Ile Ala Arg Phe Tyr
65 70

<210> 66
<211> 2581
<212> DNA
<213> Homo sapiens

<400> 66
ctttcaaccc gcgctcgccg gctccagccc cgcgcgcccc cacccccttgc cctcccggcg 60
gctccgcagg gtgaggtggc tttgaccccg ggttgcccgg ccagcacgac cgaggaggtg 120
gctggacagc tggaggatga acggagaagc cgactgcccc acagacctgg aaatggccgc 180
ccccaaaggc caagaccgtt ggtcccagga agacatgctg actttgctgg aatgcatgaa 240
gaacaacctt ccatccaatg acagctccaa gttcaaaacc accgaatcac acatggactg 300
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<212> PRT
<213> Homo sapiens

<400> 67

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Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Lys Phe Lys Thr
         35                  40                  45

Thr Glu Ser His Met Asp Trp Glu Lys Val Ala Phe Lys Asp Phe Ser
     50                  55                  60

Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
 65                  70                  75                  80
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Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Ala Gln Glu His Val
85 90 95

Lys Asn Pro Tyr Lys Gly Lys Lys Leu Lys Lys His Pro Asp Phe Pro
100 105 110

Lys Lys Pro Leu Thr Pro Tyr Phe Arg Phe Phe Met Glu Lys Arg Ala
115 120 125

Lys Tyr Ala Lys Leu His Pro Glu Met Ser Asn Leu Asp Leu Thr Lys
130 135 140

Ile Leu Ser Lys Lys Tyr Lys Glu Leu Pro Glu Lys Lys Lys Met Lys
145 150 155 160

Tyr Ile Gln Asp Phe Gln Arg Glu Lys Gln Glu Phe Glu Arg Asn Leu
165 170 175

Ala Arg Phe Arg Glu Asp His Pro Asp Leu Ile Gln Asn Ala Lys Lys
180 185 190

Ser Asp Ile Pro Glu Lys Pro Lys Thr Pro Gln Gln Leu Trp Tyr Thr
195 200 205

His Glu Lys Lys Val Tyr Leu Lys Val Arg Pro Asp Ala Thr Thr Lys
210 215 220

Glu Val Lys Asp Ser Leu Gly Lys Gln Trp Ser Gln Leu Ser Asp Lys
225 230 235 240

Lys Arg Leu Lys Trp Ile His Lys Ala Leu Glu Gln Arg Lys Glu Tyr
245 250 255

Glu Glu Ile Met Arg Asp Tyr Ile Gln Lys His Pro Glu Leu Asn Ile
260 265 270

Ser Glu Glu Gly Ile Thr Lys Ser Thr Leu Thr Lys Ala Glu Arg Gln
275 280 285

Leu Lys Asp Lys Phe Asp Gly Arg Pro Thr Lys Pro Pro Pro Asn Ser
290 295 300

Tyr Ser Leu Tyr Cys Ala Glu Leu Met Ala Asn Met Lys Asp Val Pro
305 310 315 320

Ser Thr Glu Arg Met Val Leu Cys Ser Gln Gln Trp Lys Leu Leu Ser
325 330 335

Gln Lys Glu Lys Asp Ala Tyr His Lys Lys Cys Asp Gln Lys Lys Lys
340 345 350

Asp Tyr Glu Val Glu Leu Leu Arg Phe Leu Glu Ser Leu Pro Glu Glu
355 360 365

Glu Gln Gln Arg Val Leu Gly Glu Glu Lys Met Leu Asn Ile Asn Lys

370 375 380

Lys Gln Ala Thr Ser Pro Ala Ser Lys Lys Pro Ala Gln Glu Gly Gly
385 390 395 400

Lys Gly Gly Ser Glu Lys Pro Lys Arg Pro Val Ser Ala Met Phe Ile
405 410 415

Phe Ser Glu Glu Lys Arg Arg Gln Leu Gln Glu Glu Arg Pro Glu Leu
420 425 430

Ser Glu Ser Glu Leu Thr Arg Leu Leu Ala Arg Met Trp Asn Asp Leu
435 440 445

Ser Glu Lys Lys Lys Ala Lys Tyr Lys Ala Arg Glu Ala Ala Leu Lys
450 455 460

Ala Gln Ser Glu Arg Lys Pro Gly Gly Glu Arg Glu Glu Arg Gly Lys
465 470 475 480

Leu Pro Glu Ser Pro Lys Arg Ala Glu Glu Ile Trp Gln Gln Ser Val
485 490 495

Ile Gly Asp Tyr Leu Ala Arg Phe Lys Asn Asp Arg Val Lys Ala Leu
500 505 510

Lys Ala Met Glu Met Thr Trp Asn Asn Met Glu Lys Lys Glu Lys Leu
515 520 525

Met Trp Ile Lys Lys Ala Ala Glu Asp Gln Lys Arg Tyr Glu Arg Glu
530 535 540

Leu Ser Glu Met Arg Ala Pro Pro Ala Ala Thr Asn Ser Ser Lys Lys
545 550 555 560

Met Lys Phe Gln Gly Glu Pro Lys Lys Pro Pro Met Asn Gly Tyr Gln
565 570 575

Lys Phe Ser Gln Glu Leu Leu Ser Asn Gly Glu Leu Asn His Leu Pro
580 585 590

Leu Lys Glu Arg Met Val Glu Ile Gly Ser Arg Trp Gln Arg Ile Ser
595 600 605

Gln Ser Gln Lys Glu His Tyr Lys Lys Leu Ala Glu Glu Gln Gln Lys
610 615 620

Gln Tyr Lys Val His Leu Asp Leu Trp Val Lys Ser Leu Ser Pro Gln
625 630 635 640

Asp Arg Ala Ala Tyr Lys Glu Tyr Ile Ser Asn Lys Arg Lys Ser Met
645 650 655

Thr Lys Leu Arg Gly Pro Asn Pro Lys Ser Ser Arg Thr Thr Leu Gln
660 665 670

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Ser Lys Ser Glu Ser Glu Glu Asp Asp Glu Glu Asp Glu Asp Asp Glu
        675                 680                 685

Asp Glu Asp Glu Glu Glu Glu Asp Asp Glu Asn Gly Asp Ser Ser Glu
    690                 695                 700

Asp Gly Gly Asp Ser Ser Glu Ser Ser Ser Glu Asp Glu Ser Glu Asp
705                 710                 715                 720

Gly Asp Glu Asn Glu Glu Asp Asp Glu Asp Glu Asp Asp Asp Glu Asp
                725                 730                 735

Asp Asp Glu Asp Glu Asp Asn Glu Ser Glu Gly Ser Ser Ser Ser Ser
            740                 745                 750

Ser Ser Leu Gly Asp Ser Ser Asp Phe Asp Ser Asn
        755                 760
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<210> 68
<211> 434
<212> DNA
<213> Homo sapiens

<400> 68

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<211> 244
<212> DNA
<213> Homo sapiens

<400> 69

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cgag                                                             244
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<211> 437
<212> DNA
<213> Homo sapiens

<400> 70

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tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggctgg ctgggccagg 360
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tggcgcagga agccggg 437

<210> 71
<211> 271
<212> DNA
<213> Homo sapiens

<400> 71
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gaccaatcca aggagggctg caggagggac ttcaggtgac cctccagggg actaccgaga 180
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<210> 72
<211> 290
<212> DNA
<213> Homo sapiens

<400> 72
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ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 240
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<210> 73
<211> 144
<212> PRT
<213> Homo sapiens

<400> 73
Lys Met Leu Asp Ala Glu Asp Ile Val Gly Thr Ala Arg Pro Asp Glu
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Lys Ala Ile Met Thr Tyr Val Ser Ser Phe Tyr His Ala Phe Ser Gly
20 25 30

Ala Gln Lys Ala Glu Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala
35 40 45

Val Asn Gln Glu Asn Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala
50 55 60

Ser Asp Leu Leu Glu Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asn
65 70 75 80

Arg Val Pro Glu Asn Thr Met His Ala Met Gln Gln Lys Leu Glu Asp
85 90 95

Phe Arg Asp Tyr Arg Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys
100 105 110

Cys Gln Leu Glu Ile Asn Phe Asn Thr Leu Gln Thr Lys Leu Arg Leu
115 120 125

Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp
130 135 140

<210> 74
<211> 64
<212> PRT
<213> Homo sapiens

<400> 74
Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
1 5 10 15

Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
20 25 30

Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
35 40 45

Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
50 55 60

<210> 75
<211> 145
<212> PRT
<213> Homo sapiens

<400> 75
Gly Thr Gly Ala Ser Ser Gly Thr Arg Thr Pro Asp Val Lys Ala Phe
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Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
20 25 30

Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
35 40 45

Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
50 55 60

Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro
65 70 75 80

Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
85 90 95

Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
100 105 110

Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
115 120 125

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130 135 140

Gly
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<210> 76
<211> 69
<212> PRT
<213> Homo sapiens

<400> 76
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35 40 45

Gly Leu Gln Val Thr Leu Gln Gly Thr Thr Glu Ser Phe Ala Gln Lys
50 55 60

Phe Val Val Asn Phe
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<210> 77
<211> 96
<212> PRT
<213> Homo sapiens

<400> 77
Glu Pro Tyr Pro Glu Val Ser Arg Ile Pro Thr Val Arg Gly Cys Asn
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Gly Ser Leu Ser Gly Ala Leu Ser Cys Cys Glu Asp Ser Ala Gln Gly
20 25 30

Ser Gly Pro Pro Lys Ala Pro Thr Val Ala Glu Gly Pro Ser Ser Cys
35 40 45

Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser
50 55 60

Leu Ser Cys Glu Arg Leu Arg Ala Leu Leu Pro Gln Phe Asp Gly Arg
65 70 75 80

Arg Glu Asp Met Ala Ser Val Leu Glu Met Ser Val Ala Ile Pro Ala

85 90 95

<210> 78
<211> 2076
<212> DNA
<213> Homo sapiens

<400> 78
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<212> DNA
<213> Homo sapiens

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<210> 80
<211> 1460
<212> DNA
<213> Homo sapiens

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attactaaaa cattcaaaga atcaaattta agaaatcagt tcatcagagc tcatgttgcc 360
aaactgaggc aagatggtag tggtgtgaga gcggatgttg tcatgaaatt tcaattcact 420
agaaataaca atggagcatc aatgaaaagc agaattgagt ctgttttacg acaaatgctg 480
aataactctg gaaacctgga aataaaccct tcaactgaga taacatcact tactgaccag 540
gctgcagcaa attggcttat taatgaatgt ggggccggtc cagacctaat aacattgtct 600
gagcagagaa tccttggagg cactggaggct gaggagggaa gctggccgtg gcaagtcagt 660
ctgcggctca ataatgccca ccactgtgga ggcagcctga tcaataacat gtggatcctg 720
acagcagctc actgcttcag aagcaactct aatcctcgtg actggattgc cacgtctggt 780
atttccacaa catttcctaa actaagaatg agagtaagaa atattttaat tcataacaat 840
tataaatctg caactcatga aaatgacatt gcacttgtga gacttgagaa cagtgtcacc 900
tttaccaaag atatccatag tgtgtgtctc ccagctgcta cccagaatat tccacctggc 960
tctactgctt atgtaacagg atggggcgct caagaatatg ctggccacac agttccagag 1020
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aatggagcca tcttgtctgg aatgctgtgt gctggagtac ctcaaggtgg agtggacgca 1140
tgtcagggtg actctggtgg cccactagta caagaagact cacggcggct ttggtttatt 1200
gtggggatag taagctgggg agatcagtgt ggcctgccgg ataagccagg agtgtatact 1260
cgagtgacag cctaccttga ctggattagg caacaaactg ggatctagtg caacaagtgc 1320
atccctgttg caaagtctgt atgcaggtgt gcctgtctta aattccaaag ctttacattt 1380
caactgaaaa agaaactaga aatgtcctaa tttaacatct tgttacataa atatggttta 1440
acaaaaaaaa aaaaaaaaaa                                              1460
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<210> 81
<211> 386
<212> PRT
<213> Homo sapiens

<400> 81

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Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met Gly Thr Ala
1               5                   10                  15

Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu Gln Lys Gln
            20                  25                  30

Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
        35                  40                  45

Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His
    50                  55                  60

Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile Val Gly His
65                  70                  75                  80

Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val Thr Thr Val
                85                  90                  95

Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln Cys Arg Glu
            100                 105                 110

Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile Arg Ser Asp
        115                 120                 125

Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg Phe Thr Cys
    130                 135                 140

Lys Gly Lys Pro Val His His Phe Met Asn Thr Ser Thr Phe Thr Glu
```

145 150 155 160

Tyr Thr Val Val Asp Glu Ser Ser Val Ala Lys Ile Asp Asp Ala Ala
165 170 175

Pro Pro Glu Lys Val Cys Leu Ile Gly Cys Gly Phe Ser Thr Gly Tyr
180 185 190

Gly Ala Ala Val Lys Thr Gly Lys Val Lys Pro Gly Ser Thr Cys Val
195 200 205

Val Phe Gly Leu Arg Gly Val Gly Leu Ser Val Ile Met Gly Cys Lys
210 215 220

Ser Ala Gly Ala Ser Arg Ile Ile Gly Ile Asp Leu Asn Lys Asp Lys
225 230 235 240

Phe Glu Lys Ala Met Ala Val Gly Ala Thr Glu Cys Ile Ser Pro Lys
245 250 255

Asp Ser Thr Lys Pro Ile Ser Glu Val Leu Ser Glu Met Thr Gly Asn
260 265 270

Asn Val Gly Tyr Thr Phe Glu Val Ile Gly His Leu Glu Thr Met Ile
275 280 285

Asp Ala Leu Ala Ser Cys His Met Asn Tyr Gly Thr Ser Val Val Val
290 295 300

Gly Val Pro Pro Ser Ala Lys Met Leu Thr Tyr Asp Pro Met Leu Leu
305 310 315 320

Phe Thr Gly Arg Thr Trp Lys Gly Cys Val Phe Gly Gly Leu Lys Ser
325 330 335

Arg Asp Asp Val Pro Lys Leu Val Thr Glu Phe Leu Ala Lys Lys Phe
340 345 350

Asp Leu Asp Gln Leu Ile Thr His Val Leu Pro Phe Lys Lys Ile Ser
355 360 365

Glu Gly Phe Glu Leu Leu Asn Ser Gly Gln Ser Ile Arg Thr Val Leu
370 375 380

Thr Phe
385

<210> 82
<211> 418
<212> PRT
<213> Homo sapiens

<400> 82
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro

1 5 10 15

Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30

Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45

Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60

Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80

Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95

Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110

Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125

Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140

Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160

Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175

Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190

Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205

Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220

Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240

Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255

Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270

Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285

His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300

Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305 310 315 320

Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
325 330 335

Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
340 345 350

Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
355 360 365

Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
370 375 380

Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385 390 395 400

Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
405 410 415

Gly Ile

<210> 83
<211> 418
<212> PRT
<213> Homo sapiens

<400> 83
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15

Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30

Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45

Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60

Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80

Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95

Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110

Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125

```
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140

Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160

Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175

Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190

Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205

Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220

Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240

Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255

Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270

Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285

His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300

Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320

Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335

Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350

Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365

Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380

Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400

Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
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Gly Ile

<210> 84
<211> 489
<212> DNA
<213> Homo sapiens

<400> 84
aaaagggtaa gcttgatgat taccaggaac gaatgaacaa aggggaaagg cttaatcaag 60
atcagctgga tgccgtttct aagtaccagg aagtcacaaa taatttggag tttgcaaaag 120
aattacagag gagtttcatg gcactaagtc aagatattca gaaaacaata aagaagacag 180
cacgtcggga gcagcttatg agagaagaag ctgaacagaa acgtttaaaa actgtacttg 240
agctacagta tgttttggac aaattgggag atgatgaagt gcggactgac ctgaaacaag 300
gtttgaatgg agtgccaata ttgtccgaag aggagttgtc attgttggat gaattctata 360
agctagtaga ccctgaacgg gacatgagct tgaggttgaa tgaacagtat gaacatgcct 420
ccattcacct gtgggacctg ctggaaggga aggaaaaacc tgtatgtgga accacctata 480
aagttctaa 489

<210> 85
<211> 304
<212> DNA
<213> Homo sapiens

<400> 85
gggacctgga ggaggccacg ctgcagcatg aagccacagc agccaccctg aggaagaagc 60
acgcggacag cgtggccgag ctcggggagc agatcgacaa cctgcagcgg gtgaagcaga 120
agctggagaa ggagaagagc gagatgaaga tggagatcga tgacctcgct tgtaacatgg 180
aggtcatctc caaatctaag ggaaaccttg agaagatgtg ccgcacactg gaggaccaag 240
tgagtgagct gaagacccag gaggaggaac agcagcggct gatcaatgaa ctgactgcgc 300
agag 304

<210> 86
<211> 296
<212> DNA
<213> Homo sapiens

<400> 86
gaaaatcctt cctttgaatg ggaatctcca agcagttgaa ttgggcgaaa aaagaacctc 60
ttccttaagg attaaaatgt ttagggcaac acgtgttact tccacttcca gatttctgaa 120
tccatatgtt gtatgtttcc ttgtcctccc aggggttgtg atcctggcag tccccatagc 180
tctacttgtt tacttttag cttttgatca aaaatcttac ttttattgga gcaatttcc 240
actcccaaat gttgaatata atagtccgtt taattcccc gcttcaccgg gaattc 296

<210> 87
<211> 904
<212> DNA
<213> Homo sapiens

<400> 87
gtgtccagga aacgattcat gaacataaca agcttgctgc aaattcagat catctcatgc 60
agattcaaaa atgtgagttg gtcttgatcc acacctaccc agttggtgaa gacagccttg 120
tatctgatcg ttctaaaaaa gagttgtccc cggttttaac cagtgaagtt catagtgttc 180
gtgcaggacg gcatcttgct accaaattga atattttagt acagcaacat tttgacttgg 240
cttcaactac tattacaaat attccaatga aggaagaaca gcatgctaac acatctgcca 300
attatgatgt ggagctactt catcacaaag atgcacatgt agatttcctg aaaagtggtg 360

attcgcatct aggtggcggc agtcgagaag gctcgtttaa agaaacaata acattaaagt 420
ggtgtacacc aaggacaaat aacattgaat tacactattg tactggagct tatcggattt 480
cacctgtaga tgtaaatagt agaccttcct cctgccttac taattttctt ctaaatggtc 540
gttctgtttt attggaacaa ccacgaaagt caggttctaa agtcattagt catatgctta 600
gtagccatgg aggagagatt ttttgcacg tccttagcag ttctcgatcc attctagaag 660
atccaccttc aattagtgaa ggatgtggag gaagagttac agactaccgg attacagatt 720
ttggtgaatt tatgagggga aaacagatta actccttttc tacaccccag atataaaatc 780
gatggaagtc ttgaggtccc tttggaaccg agccaaaaga tcagttaaaa aaacataccc 840
gttactggcc tatgatttca aaaacccacc atttttaaca tgcaagcggt agttccgtta 900
acca 904

<210> 88
<211> 387
<212> DNA
<213> Homo sapiens

<400> 88
cgtctctccc ccagtttgcc gttcacccgg agcgctcggg acttgccgat agtggtgacg 60
gcggcaacat gtctgtggct ttcgcggccc cgaggcagcg aggcaagggg gagatcactc 120
ccgctgcgat tcagaagatg ttggatgaca ataaccatct tattcagtgt ataatggact 180
ctcagaataa aggaaagacc tcagagtgtt ctcagtatca gcagatgttg cacacaaact 240
tggtatacct tgctacaata gcagattcta atcaaaatat gcagtctctt ttaccagcac 300
cacccacaca gaatatgcct atgggtcctg gagggatgaa tcagagcggg cctcccccac 360
ctccacgctc tcacaacatg ccttcaa 387

<210> 89
<211> 481
<212> DNA
<213> Homo sapiens

<400> 89
tgttcttgga cctgcggtgc tatagagcag gctcttctag gttggcagtt gccatggaat 60
ctggacccaa aatgttggcc cccgtttgcc tggtggaaaa taacaatgag cagctattgg 120
tgaaccagca agctatacag attcttgaaa agatttctca gccagtggtg gtggtggcca 180
ttgtaggact gtaccgtaca gggaaatcct acttgatgaa ccatctggca ggacagaatc 240
atggcttccc tctgggctcc acggtgcagt ctgaaaccaa gggcatctgg atgtggtgcg 300
tgccccaccc atccaagcca aaccacaccc tggtccttct ggacaccgaa ggtctgggcg 360
atgtggaaaa gggtgaccct aagaatgact cctggatctt tgccctggct gtgctcctgt 420
gcagcacctt tgtctacaac agcatgagca ccatcaacca ccaggccctg gagcagctgc 480
a 481

<210> 90
<211> 491
<212> DNA
<213> Homo sapiens

<400> 90
tgaaaactgt tcttggacct gcggtgctat agagcaggtt ggcagttgcc atggaatctg 60
gacccaaaat gttggccccc gtttgcctgg tggaaaataa caatgagcag ctattggtga 120
accagcaagc tatacagatt cttgaaaaga tttctcagcc agtggtggtg gtggccattg 180
taggactgta ccgtacaggg aaatcctact tgatgaacca tctggcagga cagaatcatg 240
gcttccctct gggctccacg gtgcagtctg aaaccaaggg catctggatg tggtgcgtgc 300
cccacccatc caagccaaac cacaccctgg tccttctgga caccgaaggt ctgggcgatg 360
tggaaaaggg tgaccctaag aatgactcct ggatctttgc cctggctgtg ctcctgtgca 420
gcacctttgt ctacaacagc atgagcacca tcaaccacca agccctggag cagctgcatt 480

atgtgacgga c 491

<210> 91
<211> 488
<212> DNA
<213> Homo sapiens

<400> 91
ttcgacagtc agccgcatct tcttttgcgt cgccagccga gccacatcgc tcagacacca 60
tggggaaggt gaaggtcgga gtcaacggat ttggtcgtat tgggcgcctg gtcaccaggg 120
ctgcttttaa ctctggtaaa gtggatattg ttgccatcaa tgaccccttc attgacctca 180
actacatggt ttacatgttc caatatgatt ccacccatgg caaattccat ggcaccgtcg 240
aggctgagaa cgggaagctt gtcatcaatg gaaatcccat caccatcttc caggagcgag 300
atccctccaa aatcaagtgg ggcgatgctg gcgctgagta cgtcgtggag tccactggcg 360
tcttcaccac catggagaag gctggggctc atttgcaggg gggagccaaa agggtcatca 420
tctctgcccc tctgctgatg ccccatgttc gtcatgggtg tgaaccatga gaagtatgac 480
acagcctc 488

<210> 92
<211> 384
<212> DNA
<213> Homo sapiens

<400> 92
gacagtcagc cgcatcttct tttgcgtcgc cagccgagcc acatcgctca gacaccatgg 60
ggaaggtgaa ggtcggagtc aacggatttg gtcgtattgg gcgcctggtc accagggctg 120
cttttaactc tggtaaagtg gatattgttg ccatcaatga ccccttcatt gacctcaact 180
acatggttta catgttccaa tatgattcca cccatggcaa attccatggc accgtcgagg 240
ctgagaacgg gaagcttgtc atcaatggaa atcccatcac catcttccag gagcgagatc 300
cctccaaaat caagtggggc gatactggcg ctgagtacgt cgtggagtcc actggcgtct 360
tcaccaccat ggagaaggct gggg 384

<210> 93
<211> 162
<212> PRT
<213> Homo sapiens

<400> 93
Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
1   5   10   15

Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
            20   25   30

Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
        35   40   45

Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
    50   55   60

Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
65   70   75   80

Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
                85   90   95

Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
100 105 110

Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met
115 120 125

Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
130 135 140

Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
145 150 155 160

Val Leu

<210> 94
<211> 100
<212> PRT
<213> Homo sapiens

<400> 94
Asp Leu Glu Glu Ala Thr Leu Gln His Glu Ala Thr Ala Ala Thr Leu
1 5 10 15

Arg Lys Lys His Ala Asp Ser Val Ala Glu Leu Gly Glu Gln Ile Asp
20 25 30

Asn Leu Gln Arg Val Lys Gln Lys Leu Glu Lys Glu Lys Ser Glu Met
35 40 45

Lys Met Glu Ile Asp Asp Leu Ala Cys Asn Met Glu Val Ile Ser Lys
50 55 60

Ser Lys Gly Asn Leu Glu Lys Met Cys Arg Thr Leu Glu Asp Gln Val
65 70 75 80

Ser Glu Leu Lys Thr Gln Glu Glu Glu Gln Gln Arg Leu Ile Asn Glu
85 90 95

Leu Thr Ala Gln
100

<210> 95
<211> 99
<212> PRT
<213> Homo sapiens

<400> 95
Lys Ile Leu Pro Leu Asn Gly Asn Leu Gln Ala Val Glu Leu Gly Glu
1 5 10 15

Lys Arg Thr Ser Ser Leu Arg Ile Lys Met Phe Arg Ala Thr Arg Val
20 25 30

Thr Ser Thr Ser Arg Phe Leu Asn Pro Tyr Val Val Cys Phe Leu Val
35 40 45

Leu Pro Gly Val Val Ile Leu Ala Val Pro Ile Ala Leu Leu Val Tyr
50 55 60

Phe Leu Ala Phe Asp Gln Lys Ser Tyr Phe Tyr Trp Ser Asn Phe Pro
65 70 75 80

Leu Pro Asn Val Glu Tyr Asn Ser Pro Phe Asn Ser Pro Ala Ser Pro
85 90 95

Gly Ile Pro

<210> 96
<211> 257
<212> PRT
<213> Homo sapiens

<400> 96
Val Gln Glu Thr Ile His Glu His Asn Lys Leu Ala Ala Asn Ser Asp
1 5 10 15

His Leu Met Gln Ile Gln Lys Cys Glu Leu Val Leu Ile His Thr Tyr
20 25 30

Pro Val Gly Glu Asp Ser Leu Val Ser Asp Arg Ser Lys Lys Glu Leu
35 40 45

Ser Pro Val Leu Thr Ser Glu Val His Ser Val Arg Ala Gly Arg His
50 55 60

Leu Ala Thr Lys Leu Asn Ile Leu Val Gln Gln His Phe Asp Leu Ala
65 70 75 80

Ser Thr Thr Ile Thr Asn Ile Pro Met Lys Glu Glu Gln His Ala Asn
85 90 95

Thr Ser Ala Asn Tyr Asp Val Glu Leu Leu His His Lys Asp Ala His
100 105 110

Val Asp Phe Leu Lys Ser Gly Asp Ser His Leu Gly Gly Gly Ser Arg
115 120 125

Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu Lys Trp Cys Thr Pro Arg
130 135 140

Thr Asn Asn Ile Glu Leu His Tyr Cys Thr Gly Ala Tyr Arg Ile Ser
145 150 155 160

Pro Val Asp Val Asn Ser Arg Pro Ser Ser Cys Leu Thr Asn Phe Leu
165 170 175

Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser
180 185 190

Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
195 200 205

His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile
210 215 220

Ser Glu Gly Cys Gly Gly Arg Val Thr Asp Tyr Arg Ile Thr Asp Phe
225 230 235 240

Gly Glu Phe Met Arg Gly Lys Gln Ile Asn Ser Phe Ser Thr Pro Gln
245 250 255

Ile

<210> 97
<211> 128
<212> PRT
<213> Homo sapiens

<400> 97
Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
1 5 10 15

Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
20 25 30

Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
35 40 45

Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
50 55 60

Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
65 70 75 80

Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
85 90 95

Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met
100 105 110

Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
115 120 125

<210> 98
<211> 159
<212> PRT
<213> Homo sapiens

<400> 98
Phe Leu Asp Leu Arg Cys Tyr Arg Ala Gly Ser Ser Arg Leu Ala Val
1 5 10 15

Ala Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu
20 25 30

Asn Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu
35 40 45

Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr
50 55 60

Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His
65 70 75 80

Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp
85 90 95

Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
100 105 110

Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn
115 120 125

Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val
130 135 140

Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu
145 150 155

<210> 99
<211> 147
<212> PRT
<213> Homo sapiens

<400> 99
Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
1 5 10 15

Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
20 25 30

Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
35 40 45

Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
50 55 60

Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65 70 75 80

Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu

```
                85                  90                  95

Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
            100                 105                 110

Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
        115                 120                 125

Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
    130                 135                 140

Val Thr Asp
145


&lt;210&gt; 100
&lt;211&gt; 124
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 100
Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile Gly Arg
  1               5                  10                  15

Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile Val Ala
             20                  25                  30

Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
         35                  40                  45

Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn
     50                  55                  60

Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
 65                  70                  75                  80

Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val
                 85                  90                  95

Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly Ala His Leu
            100                 105                 110

Gln Gly Gly Ala Lys Arg Val Ile Ile Ser Ala Pro
        115                 120


&lt;210&gt; 101
&lt;211&gt; 127
&lt;212&gt; PRT
&lt;213&gt; Homo sapiens

&lt;400&gt; 101
Gln Ser Ala Ala Ser Ser Phe Ala Ser Pro Ala Glu Pro His Arg Ser
  1               5                  10                  15
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Asp Thr Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile
20 25 30

Gly Arg Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile
35 40 45

Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met
50 55 60

Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
65 70 75 80

Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln
85 90 95

Glu Arg Asp Pro Ser Lys Ile Lys Trp Gly Asp Thr Gly Ala Glu Tyr
100 105 110

Val Val Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly
115 120 125

<210> 102
<211> 1225
<212> DNA
<213> Homo sapiens

<400> 102
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gcggagacgg cagccgtgac ggtggcagcg gcggcgcggg acctgggcct gggggaatga 120
ggcggccgcg gcgggccagc ggcggagccg tgtagcggag aagctccccc tccctgcttc 180
ccttggccga gccgggggcg cgcgcgcacg cggccgtcca gagcgggctc cccacccctc 240
gactcctgcg acccgcaccg cacccccacc cgggcccgga ggatgatgaa gctcaagtcg 300
aaccagaccc gcacctacga cggcgacggc tacaagaagc gggccgcatg cctgtgtttc 360
cgcagcgaga gcgaggagga ggtgctactc gtgagcagta gtcgccatcc agacagatgg 420
attgtccctg gaggaggcat ggagcccgag gaggagccaa gtgtggcagc agttcgtgaa 480
gtctgtgagg aggctggagt aaaagggaca ttgggaagat tagttggaat tttgagaac 540
caggagagga agcacaggac gtatgtctat gtgctcattg tcactgaagt gctggaagac 600
tgggaagatt cagttaacat tggaaggaag agggaatggt ttaaaataga agacgccata 660
aaagtgctgc agtatcacaa acccgtgcag gcatcatatt ttgaaacatt gaggcaaggc 720
tactcagcca acaatggcac cccagtcgtg gccaccacat actcggtttc tgctcagagc 780
tcgatgtcag gcatcagatg actgaagact tcctgtaaga gaaatggaaa ttggaaacta 840
gactgaagtg caaatcttcc ctctcaccct ggctctttcc acttctcaca ggcctcctct 900
ttcaaataag gcatggtggg cagcaaagaa agggtgtatt gataatgttg ctgtttggtg 960
ttaagtgatg gggctttttc ttctgttttt attgagggtg gggttgggt gtgtaatttg 1020
taagtacttt tgtgcatgat ctgtccctcc ctcttcccac ccctgcagtc ctctgaagag 1080
aggccaacag ccttcccctg ccttggattc tgaagtgttc ctgtttgtct tatcctggcc 1140
ctggccagac gttttctttg atttttaatt tttttttttt attaaaagat accagtatga 1200
gaaaaaaaaa aaaaaaaaac tcgag 1225

<210> 103
<211> 741
<212> DNA
<213> Homo sapiens

<400> 103
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atcaataact ggcagcaact ttcaagcttt aggggccaag agtttgtgtg ggactatgtc 120
atcctcgatg aagcacataa aataaaaacc tcatctacta agtcagcaat atgtgctcgt 180
gctattcctg caagtaatcg cctcctcctc acaggaaccc caatccagaa taatttacaa 240
gaactatggt ccctatttga tttggcttgt caagggtccc tgctgggaac attaaaaact 300
tttaagatgg agtatgaaaa tcctattact agagcaagag agaaggatgc taccccagga 360
gaaaaagcct tgggatttaa aatatctgaa aacttaatgg caatcataaa accctatttt 420
ctcaggagga ctaaagaaga cgtacagaag aaaaagtcaa gcaacccaga ggccagactt 480
aatgaaaaga atccagatgt tgatgccatt tgtgaaatgc cttccctttc caggagaaat 540
gatttaatta tttggatacg acttgtgcct ttacaagaag aaatatacag gaaatttgtg 600
tctttagatc atatcaagga gttgctaatg gagacgcgct cacctttggc tgagctaggt 660
gtcttaaaga agctgtgtga tcatcctagg ctgctgtctg cacgggcttg ttgtttgcta 720
aatcttggga cattctctgc t 741

<210> 104
<211> 321
<212> DNA
<213> Homo sapiens

<400> 104
ttgctctgcg tcatcaaaga caccaaactg ctgtgctata aaagttccaa ggaccagcag 60
cctcagatgg aactgccact ccaaggctgt aacattacgt acatcccgaa agacagcaaa 120
aagaagaagc acgagctgaa gattactcag cagggcacgg acccgcttgt tctcgccgtc 180
cagagcaagg aacaggccga gcagtggctg aaggtgatca aagaagccta cagtggttgt 240
agtggccccg tggattcaga gtgtcctcct ccaccaagct ccccggtgca caaggcagaa 300
ctggagaaga aactgtcttc a 321

<210> 105
<211> 389
<212> DNA
<213> Homo sapiens

<400> 105
cagcactggc cacactataa aattcaggtt cagaaaaaca gggtaagtca cagacagcaa 60
cgcttccagc atttattttc tttgcaccca tgggcaattt gagaaaattt acctttagaa 120
cgaactctgt taaaggtaca gacagtacaa tactttttat tcagaaggtt tctgcataaa 180
ggtgatagtc ttttgactta atatattatt gtctcctgcc ttgtgtttct ggaatgaatg 240
aaggtcatta tttagaagat aatctgggtt gtatttgtgt cgtcagattg aatttcatt 300
gcacatgcta cttaatgtct ttaccaaata ataacaaagg gaaagaaaac caaatataga 360
tgtataataa ggaaaagctg gcctataga 389

<210> 106
<211> 446
<212> DNA
<213> Homo sapiens

<400> 106
gccacatttg ccctggtcat agtttaaaca ccaggtcctg tgtcacatct ttttggtgcc 60
acaagtatca ctccattgtt cagagagtaa tgtattagtt ctgcccaatt cattcttcac 120
ttttatttct tccatttcat tagcatttat atcagctcaa gaagttaagg ttagaaaatt 180
ttccacttca aattttcagt acagaaatgt gctgtgatgt ttgacaagac tatttcatag 240
taagtgagtt aatgtttatt ggcctctgct ctcctctgtg tcagacctag gaagcctgag 300
gattacttag ttgttctgtc tctgggtcca caggcagaat ttggcccatc caaagactgg 360
ccaagtgcca aaaaaaggcc tgattaggcc ctgaaattca gtgaaattct gcctgaagaa 420

acctcttatt gaatttgaaa accata 446

<210> 107
<211> 467
<212> DNA
<213> Homo sapiens

<400> 107
ccgccgctgc cgtcgccttc ctgggattgg agtctcgagc tttcttcgtt cgttcgccgg 60
cgggttcgcg cccttctcgc gcctcggggc tgcgaggctg gggaaggggt tggagggggc 120
tgttgatcgc cgcgtttaag ttgcgctcgg ggcggccatg tcggccggcg aggtcgagcg 180
cctagtgtcg gagctgagcg gcgggaccgg aggggatgag gaggaagagt ggctctatgg 240
cgatgaagat gaagttgaaa ggccagaaga agaaaatgcc agtgctaatc ctccatctgg 300
aattgaagat gaaactgctg aaaatggtgt accaaaaccg aaagtgactg agaccgaaga 360
tgatagtgat agtgacagcg atgatgatga agatgatgtg catgtcacta taggagacat 420
taaaacggga gcaccacagt atgggagtta tggtacagca cctgtaa 467

<210> 108
<211> 491
<212> DNA
<213> Homo sapiens

<400> 108
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa 60
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 120
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 180
atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 240
ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg 300
gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 360
tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag 420
cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgagg cattttacgc 480
tgcgtcattg a 491

<210> 109
<211> 489
<212> DNA
<213> Homo sapiens

<400> 109
ctcagatagt actgaacccct ttatcaacta tgtttttttca gtctgacaac caaggcggct 60
actaagtgac taagggggcag gtagtataca gtgtggataa gcaggacaaa ggggtgattc 120
acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 180
tttattttat tttattcttt tttttttttg agatggagtc tcactcttgc ccaggctgga 240
gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc 300
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 360
tgtactttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 420
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 480
tgcccgggc 489

<210> 110
<211> 391
<212> DNA
<213> Homo sapiens

<400> 110

gcggagtccg ctggctgacc cgagcgctgg tctccgccgg gaaccctggg gcatggagag 60
gtctgagtac ctcggccgcg gcgcacgctg catcgcggag ccaggctgcc gctgtcccag 120
tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagctgg 180
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 240
cgatggagta taagggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 300
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 360
tagacctggt gatcattcga gagcagacag a 391

<210> 111
<211> 172
<212> PRT
<213> Homo sapiens

<400> 111
Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
1 5 10 15

Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
20 25 30

Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
35 40 45

Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
50 55 60

Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
65 70 75 80

Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
85 90 95

Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
100 105 110

Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
115 120 125

Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
130 135 140

Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
145 150 155 160

Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
165 170

<210> 112
<211> 247
<212> PRT
<213> Homo sapiens

<400> 112
Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr

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1               5                   10                  15

Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
            20                  25                  30

Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
        35                  40                  45

Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
    50                  55                  60

Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
65                  70                  75                  80

Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
                85                  90                  95

Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
            100                 105                 110

Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
        115                 120                 125

Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
    130                 135                 140

Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
145                 150                 155                 160

Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
                165                 170                 175

Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
            180                 185                 190

Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
        195                 200                 205

Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
    210                 215                 220

Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
225                 230                 235                 240

Asn Leu Gly Thr Phe Ser Ala
                245


<210> 113
<211> 107
<212> PRT
<213> Homo sapiens

<400> 113
Leu Leu Cys Val Ile Lys Asp Thr Lys Leu Leu Cys Tyr Lys Ser Ser
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  1               5                  10                  15

Lys Asp Gln Gln Pro Gln Met Glu Leu Pro Leu Gln Gly Cys Asn Ile
                20                  25                  30

Thr Tyr Ile Pro Lys Asp Ser Lys Lys Lys Lys His Glu Leu Lys Ile
            35                  40                  45

Thr Gln Gln Gly Thr Asp Pro Leu Val Leu Ala Val Gln Ser Lys Glu
        50                  55                  60

Gln Ala Glu Gln Trp Leu Lys Val Ile Lys Glu Ala Tyr Ser Gly Cys
 65                 70                  75                  80

Ser Gly Pro Val Asp Ser Glu Cys Pro Pro Pro Pro Ser Ser Pro Val
                    85                  90                  95

His Lys Ala Glu Leu Glu Lys Lys Leu Ser Ser
                100                 105


<210> 114
<211> 155
<212> PRT
<213> Homo sapiens

<400> 114
Glu Arg Tyr Asn Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met
  1               5                  10                  15

Asp Lys Asn Glu Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys
                20                  25                  30

Leu Gly Asp Asp Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val
            35                  40                  45

Met Thr Gly Ala Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu
        50                  55                  60

Asn Glu Trp Asp Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys
 65                 70                  75                  80

Leu Asp Ser Gln Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn
                    85                  90                  95

Ser Tyr Lys Leu Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser
                100                 105                 110

Glu Tyr Leu Lys Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser
            115                 120                 125

Ser Arg His Val Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe
        130                 135                 140

Ala Ser Gln Ile Asn Leu Ser Val Glu Asn Ala
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145 150 155

<210> 115
<211> 129
<212> PRT
<213> Homo sapiens

<400> 115
Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser Ala Gly Asn Pro Gly
1 5 10 15

Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala His Ala Ala Ser Arg
20 25 30

Ser Gln Ala Ala Ala Val Pro Val Glu Phe Gln Glu His His Leu Ser
35 40 45

Glu Val Gln Asn Met Ala Ser Glu Glu Lys Leu Glu Gln Val Leu Ser
50 55 60

Ser Met Lys Glu Asn Lys Val Ala Ile Ile Gly Lys Ile His Thr Pro
65 70 75 80

Met Glu Tyr Lys Gly Glu Leu Ala Ser Tyr Asp Met Arg Leu Arg Arg
85 90 95

Lys Leu Asp Leu Phe Ala Asn Val Ile His Val Lys Ser Leu Pro Gly
100 105 110

Tyr Met Thr Arg His Asn Asn Leu Asp Leu Val Ile Ile Arg Glu Gln
115 120 125

Thr

<210> 116
<211> 550
<212> DNA
<213> Homo sapiens

<400> 116
gaattcggca ccagcctcag agccccccag cccggctacc accccctgcg gaaaggtacc 60
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tggctcaccg ctgcctagag ccaaggagct catcctgaat gaccttcccg ccagcactcc 180
tgcctccaaa tcctgtgact cctccccgcc ccaggacgct tccaccccca ggcccagctc 240
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct 300
gaggagcccc ctgactctgt ccagtccctt caccacgtcc ttcagcctgg gctcccacag 360
cactctcaac ggagacctct ccgtgcccag ctcctacgtc agcctccacc tgtcccccca 420
ggtcagcagc tctgtggtgt acggacgctc cccgtgatg gcatttgagt ctcatcccca 480
tctccgaggg tcatccgtct cttcctccct acccagcatc cctgggggaa agccggccta 540
ctccttccac 550

<210> 117
<211> 154

<212> DNA
<213> Homo sapiens

<400> 117
ttctgaggga aagccgagtg gagtgggcga cccggcggcg gtgacaatga gttttcttgg 60
aggctttttt ggtcccattt gtgagattga tgttgccctt aatgatgggg aaaccaggaa 120
aatggcagaa atgaaaactg aggatggcaa agta 154

<210> 118
<211> 449
<212> DNA
<213> Homo sapiens

<400> 118
gaattcggca ccagggcccg cagcccgagt gtcgccgcca tggcttcgcc gcagctctgc 60
cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag 120
cctctgcagc tgctggacgc ctcctggtac ctgccgaagc tggggcgcga cgcgcgacgc 180
gagttcgagg agcgccacat cccgggcgcc gctttcttcg acatcgacca gtgcagcgac 240
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc 300
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc 360
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg 420
cttgatggcg gcctccgcca ctggctgcg 449

<210> 119
<211> 642
<212> DNA
<213> Homo sapiens

<400> 119
gaattcggca cgagcagtaa cccgaccgcc gctggtcttc gctggacacc atgaatcaca 60
ctgtccaaac cttcttctct cctgtcaaca gtggccagcc ccccaactat gagatgctca 120
aggaggagca cgaggtggct gtgctggggg cgccccacaa ccctgctccc ccgacgtcca 180
ccgtgatcca catccgcagc gagacctccg tgcccgacca tgtcgtctgg tccctgttca 240
acaccctctt catgaacccc tgctgcctgg gcttcatagc attcgcctac tccgtgaagt 300
ctagggacag gaagatggtt ggcgacgtga ccggggccca ggcctatgcc tccaccgcca 360
agtgcctgaa catctgggcc ctgattctgg gcatcctcat gaccattctg ctcatcgtca 420
tcccagtgct gatcttccag gcctatggat agatcaggag gcatcactga ggccaggagc 480
tctgcccatg acctgtatcc cacgtactcc aacttccatt cctcgccctg cccccggagc 540
cgagtcctgt atcagccctt tatcctcaca cgcttttcta caatggcatt caataaagtg 600
cacgtgtttc tggtgaaaaa aaaaaaaaaa aaaaaactcg ag 642

<210> 120
<211> 603
<212> DNA
<213> Homo sapiens

<400> 120
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gtcctccacc ccgggaacag ctccccctcc caaagtgctg accagcccgg ccaccacacc 120
catgtccacc atgtccacaa tccacacctc ctctactcca gagaccaccc acacctccac 180
agtgctgacc accacagcca ccatgacaag ggccaccaat tccacggcca caccctcctc 240
cactctgggg acgacccgga tcctcactga gctgaccaca acagccacta caactgcagc 300
cactggatcc acggccaccc tgtcctccac cccagggacc acctggatcc tcacagagcc 360
gagcactata gccaccgtga tggtgcccac cggttccacg gccaccgcct cctccactct 420
gggaacagct cacaccccca aagtggtgac caccatggcc actatgccca cagccactgc 480

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ctccacggtt cccagctcgt ccaccgtggg gaccacccgc acccctgcag tgctccccag 540
cagcctgcca accttcagcg tgtccactgt gtcctcctca gtcctcacca ccctgagacc 600
cac                                                               603

<210> 121
<211> 178
<212> PRT
<213> Homo sapiens

<400> 121
Ser Glu Pro Pro Ser Pro Ala Thr Thr Pro Cys Gly Lys Val Pro Ile
 1               5                  10                  15

Cys Ile Pro Ala Arg Arg Asp Leu Val Asp Ser Pro Ala Ser Leu Ala
            20                  25                  30

Ser Ser Leu Gly Ser Pro Leu Pro Arg Ala Lys Glu Leu Ile Leu Asn
        35                  40                  45

Asp Leu Pro Ala Ser Thr Pro Ala Ser Lys Ser Cys Asp Ser Ser Pro
    50                  55                  60

Pro Gln Asp Ala Ser Thr Pro Arg Pro Ser Ser Ala Ser His Leu Cys
65                  70                  75                  80

Gln Leu Ala Ala Lys Pro Ala Pro Ser Thr Asp Ser Val Ala Leu Arg
                85                  90                  95

Ser Pro Leu Thr Leu Ser Ser Pro Phe Thr Thr Ser Phe Ser Leu Gly
            100                 105                 110

Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val
        115                 120                 125

Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
    130                 135                 140

Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser
145                 150                 155                 160

Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
                165                 170                 175

Phe His


<210> 122
<211> 36
<212> PRT
<213> Homo sapiens

<400> 122
Met Ser Phe Leu Gly Gly Phe Phe Gly Pro Ile Cys Glu Ile Asp Val
 1               5                  10                  15
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Ala Leu Asn Asp Gly Glu Thr Arg Lys Met Ala Glu Met Lys Thr Glu
            20                  25                  30

Asp Gly Lys Val
        35


<210> 123
<211> 136
<212> PRT
<213> Homo sapiens

<400> 123
Met Ala Ser Pro Gln Leu Cys Arg Ala Leu Val Ser Ala Gln Trp Val
  1               5                  10                  15

Ala Glu Ala Leu Arg Ala Pro Arg Ala Gly Gln Pro Leu Gln Leu Leu
            20                  25                  30

Asp Ala Ser Trp Tyr Leu Pro Lys Leu Gly Arg Asp Ala Arg Arg Glu
        35                  40                  45

Phe Glu Glu Arg His Ile Pro Gly Ala Ala Phe Phe Asp Ile Asp Gln
    50                  55                  60

Cys Ser Asp Arg Thr Ser Pro Tyr Asp His Met Leu Pro Gly Ala Glu
65                  70                  75                  80

His Phe Ala Glu Tyr Ala Gly Arg Leu Gly Val Gly Ala Ala Thr His
                85                  90                  95

Val Val Ile Tyr Asp Ala Ser Asp Gln Gly Leu Tyr Ser Ala Pro Arg
            100                 105                 110

Val Trp Trp Met Phe Arg Ala Phe Gly His His Ala Val Ser Leu Leu
        115                 120                 125

Asp Gly Gly Leu Arg His Trp Leu
    130                 135


<210> 124
<211> 133
<212> PRT
<213> Homo sapiens

<400> 124
Met Asn His Thr Val Gln Thr Phe Phe Ser Pro Val Asn Ser Gly Gln
  1               5                  10                  15

Pro Pro Asn Tyr Glu Met Leu Lys Glu Glu His Glu Val Ala Val Leu
            20                  25                  30

Gly Ala Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile
        35                  40                  45
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Arg Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn
     50                  55                  60

Thr Leu Phe Met Asn Pro Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr
65                  70                  75                  80

Ser Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala
                85                  90                  95

Gln Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile
            100                 105                 110

Leu Gly Ile Leu Met Thr Ile Leu Leu Ile Val Ile Pro Val Leu Ile
        115                 120                 125

Phe Gln Ala Tyr Gly
    130


<210> 125
<211> 195
<212> PRT
<213> Homo sapiens

<400> 125
Thr Thr Ala Thr Thr Thr Ala Ser Thr Gly Ser Thr Ala Thr Pro Ser
  1               5                  10                  15

Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
            20                  25                  30

Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
        35                  40                  45

Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
    50                  55                  60

Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
65                  70                  75                  80

Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
                85                  90                  95

Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
            100                 105                 110

Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
        115                 120                 125

Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
    130                 135                 140

Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
145                 150                 155                 160
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Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
                165                 170                 175

Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
            180                 185                 190

Leu Arg Pro
        195


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      <211> 509
      <212> DNA
      <213> homo sapien

      <400> 126
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actgcagcct gggagctcta ttccacctta caacaccgag gtgactgaga ccaccattgt     180
gatcacatgg acgcctgctc caagaattgg ttttaagctg ggtgtacgac caagccaggg     240
aggagaggca ccacgagaag tgacttcaga ctcaggaagc atcgttgtgt ccggcttgac     300
tccaggagta gaatacgtct acaccatcca agtcctgaga gatggacagg aaagagatgc     360
gccaattgta aacaaagtgg tgacaccatt gtctccacca acaaacttgc atctggaggc     420
aaaccctgac actggagtgc tcacagtctc ctggagagga gcaccacccc agacattact     480
gggtatagaa ttaccacaac ccctacaaa                                       509

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      <211> 500
      <212> DNA
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      <400> 127
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ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat caggcatgaa gtcatcaata     180
tcaacctgaa aaataagcct gagtggttct ttaagaaaaa tccctttggt ctggtgccag     240
ttctggaaaa cagtcagggt cagctgatct acgagtctgc catcacctgt gagtacctgg     300
atgaagcata cccagggaag aagctgttgc cggatgaccc ctatgagaaa gcttgccaga     360
agatgatctt agagttgttt tctaaggtgc catccttggt aggaagcttt attagaagcc     420
aaaataaaga agactatgct ggcctaaaag aagaatttcg taaagaattt accaagctag     480
aggaggttct gactaataag                                                 500

      <210> 128
      <211> 500
      <212> DNA
      <213> homo sapien

      <400> 128
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tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctattttc     180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt     240
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact     300
ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca     360
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ttgggcggct ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 420
atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca 500

<210> 129
<211> 497
<212> DNA
<213> homo sapien

<400> 129
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cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
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ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acctgga 497

<210> 130
<211> 383
<212> DNA
<213> homo sapien

<400> 130
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gcgggtgccc gaggcgcggc ccaacagcat ggtggtggaa caccccgagt tcctcaaggc 240
agggaaggag cctggcctgc agatctggcg tgtggagaaa gttcgatctg gtggcccgtg 300
cccaccaacc tttatggaga cttcttcacg ggcgacgcct acgtcatcct gaagacagtg 360
cagcttaaga acggaaaatc ttg 383

<210> 131
<211> 509
<212> DNA
<213> homo sapien

<400> 131
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agacaccatg ggcaaggtga aggtcggagt caacggattt ggtcgtattg ggcgcctggt 120
caccagggct gcttttaact ctggtaaagt ggatattgtt gccatcaatg accccttcat 180
tgacctcaac tacatggttt acatgttcca atatgattcc acccatggca aattccatgg 240
caccgtcaag gctgagaacg ggaagcttgt catcaatgga aatcccatca ccatcttcca 300
ggagcgagat ccctccaaaa tcaagtgggg cgatgctggc gctgagtacg tcgtggagtc 360
cactggcgtc cttcaccacc atggagaagg ctggggctca tttgcagggg ggagccaaaa 420
gggtcatcat ctctgccccc tctgctgacg cccccatgtt cgtcatgggt gtgaaccatg 480
agaagtatga caacagcctc aagatcatc 509

<210> 132
<211> 357
<212> DNA
<213> homo sapien

<400> 132
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aatctgggtc tgagttgaag aagcctgggg cctcagtgaa ggtttcctgc aaggcttctg 180
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agtggatggg atggatcaaa gtcgacactg cgaacccaac gtatgcccag ggcttcacag 300
gacgatttgt cttctccctg gacacctctg tcagcacggc atatctgcag atcagca 357

<210> 133
<211> 468
<212> DNA
<213> homo sapien

<400> 133
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gccgcgggga gccccgcttc atctcagtgg gctacgtgga cgacacgcag ttcgtgaggt 180
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ggccggagta ttgggaccgg aacacacaga tcttcaagac caacacacag actgaccgag 300
agagcctgcg gaacctgcgc ggctactaca accagagcga ggccgggtct cacaccctcc 360
agagcatgta cggctgcgac gtggggccgg acgggcgcct cctccgcggg cataaccagt 420
acgcctacga cggcaaggat tacatcgccc tgaacgagga cctgcgct 468

<210> 134
<211> 214
<212> DNA
<213> homo sapien

<400> 134
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agtgcctggt tctcttgctc caccaggaac aagccaccat gtctcgccag tcaagtgtgt 120
ccttccggag cgggggcagt cgtagcttca gcaccgcctc tgccatcacc ccgtctgtct 180
cccgcaccag cttcacctcc gtgtcccggt ccgg 214

<210> 135
<211> 355
<212> DNA
<213> homo sapien

<400> 135
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aagggcgccg ggtctgtgtt ccgcgcgcac gtgaagcacc gtaaaggcgc tgcgcgcctg 120
cgcgccgtgg atttcgctga gcggcacggc tacatcaagg gcatcgtcaa ggacatcatc 180
cacgacccgg gccgcggcgc gcccctcgcc aaggtggtct tccgggatcc gtatcggttt 240
aagaagcgga cggagctgtt cattgccgcc gagggcattc acacgggcca gtttgtgtat 300
tgcggcaaga aggcccagct caacattggc aatgtgctcc ctgtgggcac catgc 355

<210> 136
<211> 242
<212> DNA
<213> homo sapien

<400> 136
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gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 120

agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 180
aagtgccgag attgcagctc tctgcccggc cgccacccct gtctgggaag tgaggatgct 240
gt 242

<210> 137
<211> 424
<212> DNA
<213> homo sapien

<400> 137
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gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa 420
ggcc 424

<210> 138
<211> 448
<212> DNA
<213> homo sapien

<400> 138
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agacttacct gtcctactca ccgatttgaa gattcaatat actaagatct tcataaacaa 120
tgaatggcat gattcagtga gtggcaagaa atttcctgtc tttaatcctg caactgagga 180
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aagacaggct tttcagattg gatccccgtg gcgtactatg gatgcttccg agagggggcg 300
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agtcaatgaa tggtggaaaa ctctattcca atgcatatct gaatgattta gcaggctgca 420
tcaaaacatt gcgctactgt gcaggttg 448

<210> 139
<211> 510
<212> DNA
<213> homo sapien

<400> 139
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ccccaaggag ctgcgcaagt gctgcgagga cggcatgcgg gagaacccca tgaggttctc 120
gtgccagcgc cggacccgtt tcatctccct ggcgaggcgt gcaagaaggt cttcctggac 180
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gagcatgtcg gacaagaaag ggatctgtgt ggcagacccc ttcgaggtca cagtaatgca 480
ggacttcttc atcgacctgc ggctacccta 510

<210> 140
<211> 360
<212> DNA
<213> homo sapien

<400> 140
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ctcacacacc ggcctcagcc cgcaccggca gtagaagatg gtgaaagaaa caacttacta 120
cgatgttttg gggtcaaac ccaatgctac tcaggaagaa ttgaaaaagg cttataggaa 180
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ttctcaagct tacgaagttc tctctgatgc aaagaaaagg gaattatatg acaaaggagg 300
agaacaggca attaaagagg gtggagcagg tggcggtttt ggctccccca tggacatctt 360

<210> 141
<211> 483
<212> DNA
<213> homo sapien

<400> 141
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tcttcgtgaa gaccctgact ggtaagacca tcaccctcga ggtggagccc agtgacacca 420
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tga 483

<210> 142
<211> 500
<212> DNA
<213> homo sapien

<400> 142
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gccggcgagc ccggtccccg ccggcaccat gcttcccttg tcactgctga agacggctca 120
gaatcacccc atgttggtgg agctgaaaaa tggggagacg tacaatggac acctggtgag 180
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aggcctgcag cagcagaagc agcagaaagg ccgcggcatg ggcggcgctg gccgaggtgt 420
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gcctggcaga caggcgggca 500

<210> 143
<211> 400
<212> DNA
<213> homo sapien

<400> 143
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ctgcgggctg cttcgggcca gggtcgaccc gagggccagc gcaagcagcg gcaacaggag 180
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cagcatcaca gattataacc ctccgtaaat catctgcatc ccagctccca tcaaaagcca 300
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gtttgcacaa catttgcatc tacttgggac aaagcaagaa 400

<210> 144

<211> 243
<212> DNA
<213> homo sapien

<400> 144
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gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 120
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 180
aagtgccgag attgcagcct ctgcccggcc gtcaccccgt ctgggaagtg aggagcgttt 240
ctg 243

<210> 145
<211> 450
<212> DNA
<213> homo sapien

<400> 145
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cttcaagcag attggtatta ttaagacaaa caagaaaacg ggacagccca tgattaattt 360
gtacacagac agggaaactg gcaagctgaa gggagaggca acggtctctt ttgatgaccc 420
accttcagct aaagcagcct attgactggt 450

<210> 146
<211> 451
<212> DNA
<213> homo sapien

<400> 146
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gcggcagcgc aggctgacaa gcccaacagc aagcgctcac ggcggcagcg caacaacgag 420
aaccgtgaga acgcgtccag caaccacgac c 451

<210> 147
<211> 400
<212> DNA
<213> homo sapien

<400> 147
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cagcatcaca gattataacc ctccgtaaat catctgcatc ccagctccca tcaaaagcca 300
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gtttgcacaa catttgcatc tacttgggac aaagcaagaa 400

<210> 148
<211> 503
<212> DNA
<213> Homo sapien

<400> 148
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ctgcagaggc ccactgggct gtgagggtgg aagaaaaggc caaatttgat gggattttg 420
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actcaaagct gcctcttgat gtc 503

<210> 149
<211> 1061
<212> DNA
<213> homo sapien

<400> 149
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aggagaaaaa tcacgtaaaa aaaaaaaaaa aaaaactcga g 1061

<210> 150
<211> 781
<212> DNA
<213> homo sapien

<400> 150
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cccgaagggt gaagaacgac ctactcagaa tgagaagagg aaggagaaaa acataaaaag 180
aggaggcaat cgctttgagc catattccaa cccaactaaa agatacagag ccttcattac 240
aaatatacct tttgatgtga aatggcagtc acttaaagac ctggttaaag aaaaagttgg 300
tgaggtaaca tacgtggagc tcttaatgga cgctgaagga aagtcaaggg gatgtgctgt 360
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tctgagtgga aggccactga aagtcaagga agatcctgat ggtgaacatg caaggagagc 480

aatgcaaaag gctggaagac ttggaagcac agtatttgta gcaaatctgg attataaagt 540
tggctggaag aaactgaagg aagtatttag tatggctggt gtggtggtcc gagcagacat 600
tctggaagat aaagatggga aaagtcgtgg aataggcatt gtgacttttg aacagtccat 660
tgaagctgtg caagcaatat ctatgtttaa tggccagttg ctgtttgata gaccgatgca 720
cgtcaagatg gatgagaggg ctttaccaaa gggagacttt tttcctcctg aacgccacag 780
c 781

<210> 151
<211> 3275
<212> DNA
<213> Homo sapien

<400> 151
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gtttgaggaa gcaagttgga cctgcactcc agcctgtgga gatgaaccta ggactgtgat 120
tctgctatcc agtatgttgg ctgaccacag gctcaaactg gaggattata aggatcgcct 180
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<210> 158
<211> 2114
<212> DNA
<213> homo sapien

<400> 158
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gacacctcag cagcgcacca ggtggtttta ggagaaaact tgatagccac agccctttgt 180
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taccaggagg tcctggacaa acagaggcaa gtggagaatc agctccaagt gcaattaaag 660
cagcttcagc aaaggagaga agaggaaatg aagaatcacc aggagatatt aaaggctatt 720
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cgggagtact tcta 2114

<210> 159
<211> 278
<212> DNA
<213> homo sapien

<400> 159
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tgcagaatga gaatcactcc taaaataggt aatggtaaaa attaaattga caattacctc 180
tctctatgca gaaggaaata tcacctatat gacatcatca tcatctattg atacttgctg 240
gcagtgctaa taatggtttt aatgccaatt tgtaagaa 278

<210> 160
<211> 848
<212> DNA
<213> homo sapien

<400> 160
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catctacagc atgaggttct gcccgtttgc tgagaggacg cgtctagtcc tgaaggccaa 180
gggaatcagg catgaagtca tcaatatcaa cctgaaaaat aagcctgagt ggttctttaa 240
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gtctgccatc acctgtgagt acctggatga agcataccca gggaagaagc tgttgccgga 360
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cttggtagga agctttatta gaagccaaaa taaagaagac tatgctggcc taaaagaaga 480
atttcgtaaa gaatttacca agctagagga ggttctgact aataagaaga cgaccttctt 540
tggtggcaat tctatctcta tgattgatta cctcatctgg ccctggtttg aacggctgga 600
agcaatgaag ttaaatgagt gtgtagacca cactccaaaa ctgaaactgt ggatggcagc 660
catgaaggaa gatcccacag tctcagccct gcttactagt gagaaagact ggcaaggttt 720
cctagagctc tacttacaga acagccctga ggcctgtgac tatgggctct gaaggggca 780
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aactcgag 848

<210> 161
<211> 432
<212> DNA
<213> homo sapien

<400> 161

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ggaagggaag ggcccaagta aagcacagcg cgggagccta gagcacatga agctgatcct 180
gcgtgataag gagaaggagg tggaatgtca gcaggagcat atccatgaac tccaggagct 240
caaagaccag ctggagcagc agctccaggg cctgcacagg aaggtaggtg agaccagcct 300
cctcctgtcc cagcgagagc aggaaatagt ggtcctgcag cagcaactgc aggaagccag 360
ggaacaaggg gagctgaagg agcagtcact tcagagtcaa ctggatgagg cccagagagc 420
cctagcccag ag 432

<210> 162
<211> 433
<212> DNA
<213> homo sapien

<400> 162

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ttcaagctgg gagagggctc tagtccctgg ttctgaacac tctggggttc tcgggtgcag 120
gccgccatga gcaaacggaa ggcgccgcag gagactctca acgggggaat caccgacatg 180
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gctaagaaat tgcctggagt aggaacaaaa attgctgaaa agattgatga gtttttagca 360
actggaaaat tacgtaaact ggaaaagatt cggcaggatg atacgagttc atccatcaat 420
ttcctgactc gag 433

<210> 163
<211> 432
<212> DNA
<213> homo sapien

<400> 163

gaattcggca ccagatgagg ccaacgaggt gacggacagc gcgtacatgg gctccgagag 60
cacctacagt gagtgtgaga ccttcacgga cgaggacacc agcaccctgg tgcaccctga 120
gctgcaacct gaaggggacg cagacagtgc cggcggctcg gccgtgccct ctgagtgcct 180
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ccccgctttc ctcacgccca gtccgacaaa gcggctctcc agcaagaagg tggcaaggta 420
cctgcaccag tc 432

<210> 164
<211> 395
<212> DNA
<213> homo sapien

<400> 164

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gaggttcagg tggaaggtta taattacact ggcatgggaa attccaccaa taaaaaagat 180
gcacaaagca atgctgccag agactttgtt aactatttgg ttcgaataaa tgaaataaag 240
agtgaagaag ttccagcttt tggggtagca tctccgcccc cacttactga tactcctgac 300
actacagcaa atgctgaagg catcttgttg acatcgaata tgactttgat aataaatacc 360
ggttcctgaa aaaaaaaaaa aaaaaaaaac tcgag 395

<210> 165
<211> 503
<212> DNA
<213> homo sapien

<400> 165
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acagctcggc gctccttccc gctccctcac acaccggcct cagcccgcac cggcagtaga 120
agatggtgaa agaaacaact tactacgatg ttttggggt caaacccaat gctactcagg 180
aagaattgaa aaaggcttat aggaaactgg ccttgaagta ccatcctgat aagaacccaa 240
atgaaggaga gaagtttaaa cagatttctc aagcttacga agttctctct gatgcaaaga 300
aaagggaatt atatgacaaa ggaggagaac aggcaattaa agagggtgga gcaggtggcg 360
gttttggctc ccccatggac atctttgata tgttttttgg aggaggagga aggatgcaga 420
gagaaaggag aggtaaaaat gttgtacatc agctctcagt aaccctagaa gacttatata 480
atggtgcaac aagaaaactg gct 503

<210> 166
<211> 893
<212> DNA
<213> homo sapien

<400> 166
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gctgggccag aggtgccaac atggggaaac tgaggctcgg ctcggaaggg tgagagtgag 120
actacatctc aaaaaaaaaa aaaaaaaaaa aaaagaaaga aaagaaaaga aaaaagaaag 180
aacggaagta gttgtaggta gtggtatggt ggtatgagtc tgttttctgt tacttataac 240
aacaacaaca acaaaaaacg ctgaaactgg gtaatttata aagaaaagga aaaaaagcag 300
aaaaaaatca ggaagaagag aaaggaaaag aagacaaata aatgaaattt atgtattaca 360
gttctgaagg ctgagacatc ccaggtcaag ggtccacact tggcgagggc tttcttgctg 420
gtggagactc tttgtggagt cctgggacag tgcagaagga tcacgcctcc ctaccgctcc 480
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ccttcctggg ggccttggct ttgatctaca atgaagccct caagggctga aaataaatag 780
ggaagatgga gacaccctct ggggtcctc tctgagtcaa atccagtggt gggtaattgt 840
acaataaatt ttttttggtc aaatttaaaa aaaaaaaaaa aaaaaaactc gag 893

<210> 167
<211> 549
<212> DNA
<213> homo sapien

<400> 167
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ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa 420
ggccgcctac gaggccgagc tcggggatgc ccgcaagacc cttgactcag tagccaagga 480
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gcgcaatac 549

<210> 168
<211> 547
<212> DNA
<213> homo sapien

<400> 168
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tcaaaatgga ggaagagagc ggcgcgcccg gcgtgccgag cggcaacggg gctccgggcc 120
ctaagggtga aggagaacga cctgctcaga atgagaagag gaaggagaaa aacataaaaa 180
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caaacatacc ttttgatgtg aaatggcagt cacttaaaga cctggttaaa gaaaaagttg 300
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gtctgagcgg aagaccactg aaagtcaaag aagatcctga tggtgaacat gccaggagag 480
caatgcaaaa ggctggaaga cttggaagca cagtatttgt agcaaatctg gattataaag 540
ttggctg 547

<210> 169
<211> 547
<212> DNA
<213> homo sapien

<400> 169
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aaaactgtga gatggtgtgc agtgtcggag catgaggcca ctaagtgcca gagtttccgc 180
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gatagtggct tccagatgaa ccagcttcga ggcaagaagt cctgccacac gggtctaggc 480
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aaacctc 547

<210> 170
<211> 838
<212> DNA
<213> homo sapien

<400> 170
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cagcatgagg ttctgcccgt ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat 180
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gaagttaaat gagtgtgtag accacactcc aaaactgaaa ctgtggatgg cagccatgaa 660
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gctctactta cagaacagcc ctgaggcctg tgactatggg ctctgaaggg ggcaggagtc 780
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<210> 171
<211> 547
<212> DNA
<213> homo sapien

<400> 171
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gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag gcatccctcc 180
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gaccctg 547

<210> 172
<211> 608
<212> DNA
<213> homo sapien

<400> 172
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caccctcatc tacaatggtg ccctgccatg tcagtgcaac cctcaaggtt cactgagttc 120
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ggacccatca aggccaggtg gccggtgcca actgtgtgag tgcagtggga acattgaccc 540
aatggatcct gatgcctgtg acccccacac ggggcaatgc ctgcgctgtt tacaccacac 600
agagggtc 608

<210> 173
<211> 543
<212> DNA
<213> homo sapien

<400> 173
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acc 543

<210> 174
<211> 548
<212> DNA

<213> homo sapien

<400> 174
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aatgatta 548

<210> 175
<211> 604
<212> DNA
<213> homo sapien

<400> 175
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ggaccagctg agccacctga agcagtatga acgcagcatc gtggactaca agcccaacct 480
ggacctgctg gagcagcagc accagcttat ccaggaggcc ctcatcttcg acaacaagca 540
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ccgg 604

<210> 176
<211> 486
<212> DNA
<213> homo sapien

<400> 176
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ccagaacgtc acccagaatg acacaggatt ctatacccta caagtcataa agtcagatct 300
tgtgaatgaa gaagcaaccg gacagttcca tgtatacccg gagctgccca agccctccat 360
ctccagcaac aactccaacc ccgtggagga caaggatgct gtggccttca cctgtgaacc 420
tgaggttcag aacacaacct acctgtggtg ggtaaatggt cagagcctcc cggtcagtcc 480
caaggc 486

<210> 177
<211> 387
<212> DNA
<213> homo sapien

<400> 177
gaattcggca ccagggacag cagaccagac agtcacagca gccttgacaa aacgttcctg 60

```
gaactcaagc tcttctccac agaggaggac agagcagaca gcagagacca tggagtctcc     120
ctcggcccct ccccacagat ggtgcatccc ctggcagagg ctcctgctca cagcctcact     180
tctaaccttc tggaacccgc ccaccactgc caagctcact attgaatcca cgccgttcaa     240
tgtcgcagag gggaaggagg tgcttctact tgtccacaat ctgccccagc atctttttgg     300
ctacagctgg tacaaaggtg aaagagtgga tggcaaccgt caaattatag gatatgtaat     360
aggaactcaa caagctaccc cagggcc                                         387
```

<210> 178
<211> 440
<212> DNA
<213> homo sapien

<400> 178

```
gaattcggca cgaggagaag cagaaaaaca aggaatttag ccagacttta gaaaatgaga      60
aaaatacctt actgagtcag atatcaacaa aggatggtga actaaaaatg cttcaggagg     120
aagtaaccaa aatgaacctg ttaaatcagc aaatccaaga agaactctct agagttacca     180
aactaaagga gacagcagaa gaagagaaag atgatttgga agagaggctt atgaatcaat     240
tagcagaact taatggaagc attgggaatt actgtcagga tgttacagat gcccaaataa     300
aaaatgagct attggaatct gaaatgaaga accttaaaaa gtgtgtgagt gaattggaag     360
aagaaaagca gcagttagtc aaggaaaaaa ctaaggtgga atcagaaata cgaaaggaat     420
atttggagaa aatacaaggt                                                 440
```

<210> 179
<211> 443
<212> DNA
<213> homo sapien

<400> 179

```
gaattcggca ccagcggggg gctacggcgg cggctacggc ggcgtcctga ccgcgtccga      60
cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc     120
ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg     180
cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac     240
catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct     300
gcagatcgac aacgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca     360
ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct     420
gaccctggcc aggaccgacc tgg                                             443
```

<210> 180
<211> 403
<212> DNA
<213> homo sapien

<400> 180

```
gaattcggca cgaggttatg agagtcgact tcaatgttcc tatgaagaac aaccagataa      60
caaacaacca gaggattaag gctgctgtcc caagcatcaa attctgcttg gacaatggag     120
ccaagtcggt agtccttatg agccacctag gccggcctga tggtgtgccc atgcctgaca     180
agtactcctt agagccagtt gctgtagaac tcagatctct gctgggcaag gatgttctgt     240
tcttgaagga ctgtgtaggc ccagaagtgg agaaagcctg tgccaaccca gctgctgggt     300
ctgtcatcct gctggagaac ctccgctttc atgtggagga agaagggaag ggaaaagatg     360
cttctgggaa caaggttaaa gccgagccag ccaaaataga agc                       403
```

<210> 181
<211> 493
<212> DNA
<213> homo sapien

<400> 181

```
gaattcggca ccagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct    60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat   120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc   180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat   240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta   300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg   360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca   420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct   480
tacgtatgtt acc                                                      493
```

<210> 182
<211> 209
<212> PRT
<213> homo sapien

<400> 182

```
Ala Phe Ser Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly
1               5                   10                  15
Ala Leu Gln Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr
            20                  25                  30
Ala Lys Lys Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe
        35                  40                  45
Pro Tyr Ala Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val Leu
    50                  55                  60
Arg Thr Leu Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val Arg Val
65                  70                  75                  80
Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu
                85                  90                  95
Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr
            100                 105                 110
Arg Gln Val His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp Cys Glu
        115                 120                 125
Ile Thr Ala His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys
    130                 135                 140
Val Leu Gln Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp Arg Tyr
145                 150                 155                 160
Arg Gln Asp Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln Ala Glu
                165                 170                 175
Tyr Gln Val Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp Glu Gly
            180                 185                 190
Tyr Phe Gln Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys Glu Leu
        195                 200                 205
Arg
```

<210> 183
<211> 255
<212> PRT
<213> homo sapien

<400> 183

```
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Pro
1               5                   10                  15
```

Lys Met Glu Glu Glu Ser Gly Ala Pro Cys Val Pro Ser Gly Asn Gly
20 25 30
Ala Pro Gly Pro Lys Gly Glu Glu Arg Pro Thr Gln Asn Glu Lys Arg
35 40 45
Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser
50 55 60
Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp
65 70 75 80
Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu
85 90 95
Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
100 105 110
Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
115 120 125
Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
130 135 140
Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
145 150 155 160
Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
165 170 175
Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
180 185 190
Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
195 200 205
Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
210 215 220
Asn Gly Gln Leu Leu Phe Asp Arg Pro Met His Val Lys Met Asp Glu
225 230 235 240
Arg Ala Leu Pro Lys Gly Asp Phe Phe Pro Pro Glu Arg His Ser
245 250 255

<210> 184
<211> 188
<212> PRT
<213> Homo sapien

<400> 184
Leu Ser Gly Ser Cys Ile Arg Arg Glu Gln Thr Pro Glu Lys Glu Lys
1 5 10 15
Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
20 25 30
Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
35 40 45
His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
50 55 60
His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
65 70 75 80
Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
85 90 95
Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
100 105 110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
115 120 125
Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
130 135 140

Asp Phe Lys Gly Gly Leu Asn Gly Ala Val Tyr Leu Pro Ser Lys Glu
145 150 155 160
Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn
165 170 175
Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val
180 185

<210> 185
<211> 746
<212> PRT
<213> Homo sapien

<400> 185
Asp Lys His Leu Lys Asp Leu Leu Ser Lys Leu Leu Asn Ser Gly Tyr
1 5 10 15
Phe Glu Ser Ile Pro Val Pro Lys Asn Ala Lys Glu Lys Glu Val Pro
20 25 30
Leu Glu Glu Glu Met Leu Ile Gln Ser Glu Lys Lys Thr Gln Leu Ser
35 40 45
Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
50 55 60
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
65 70 75 80
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
85 90 95
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
100 105 110
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
115 120 125
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
130 135 140
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
145 150 155 160
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
165 170 175
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
180 185 190
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
195 200 205
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
210 215 220
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
225 230 235 240
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
245 250 255
Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser
260 265 270
Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro
275 280 285
Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln
290 295 300
Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys
305 310 315 320
Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe
325 330 335

```
Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro
            340                 345                 350
Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys
        355                 360                 365
Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln
    370                 375                 380
Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile
385                 390                 395                 400
Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala
                405                 410                 415
Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu
            420                 425                 430
Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly
        435                 440                 445
Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr
    450                 455                 460
Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser
465                 470                 475                 480
Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg
                485                 490                 495
Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser
            500                 505                 510
Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr
        515                 520                 525
Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys
    530                 535                 540
Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp
545                 550                 555                 560
Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe
                565                 570                 575
Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val
            580                 585                 590
Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val
        595                 600                 605
Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr
    610                 615                 620
Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu
625                 630                 635                 640
Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe
                645                 650                 655
Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys
            660                 665                 670
Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu
        675                 680                 685
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
    690                 695                 700
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
705                 710                 715                 720
Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser
                725                 730                 735
Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
            740                 745
```

<210> 186
<211> 705

<212> PRT
<213> Homo sapien

<400> 186
Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu
1 5 10 15
Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
20 25 30
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
35 40 45
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
50 55 60
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
65 70 75 80
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
85 90 95
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
100 105 110
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
115 120 125
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
130 135 140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
145 150 155 160
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
165 170 175
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
180 185 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
195 200 205
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
210 215 220
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
225 230 235 240
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
245 250 255
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
260 265 270
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
275 280 285
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
290 295 300
Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys
305 310 315 320
Gly Val Ile Phe Ala Thr Tyr Ser Ser Leu Ile Gly Glu Ser Gln Ser
325 330 335
Gly Gly Lys Tyr Lys Thr Arg Leu Lys Gln Leu Leu His Trp Cys Gly
340 345 350
Asp Asp Phe Asp Gly Val Ile Val Phe Asp Glu Cys His Lys Ala Lys
355 360 365
Asn Leu Cys Pro Val Gly Ser Ser Lys Pro Thr Lys Thr Gly Leu Ala
370 375 380
Val Leu Glu Leu Gln Asn Lys Leu Pro Lys Ala Arg Val Val Tyr Ala
385 390 395 400
Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ala Tyr Met Asn Arg

405 410 415
Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Glu Phe Ser Asp Phe
420 425 430
Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
435 440 445
Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
450 455 460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
465 470 475 480
Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
485 490 495
Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
500 505 510
Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
515 520 525
Tyr Leu Cys Ile Ala Ser Lys Val Lys Arg Val Val Gln Leu Ala Arg
530 535 540
Glu Glu Ile Lys Asn Gly Lys Cys Val Val Ile Gly Leu Gln Ser Thr
545 550 555 560
Gly Glu Ala Arg Thr Leu Glu Ala Leu Glu Glu Gly Gly Gly Glu Leu
565 570 575
Asn Asp Phe Val Ser Thr Ala Lys Gly Val Leu Gln Ser Leu Ile Glu
580 585 590
Lys His Phe Pro Ala Pro Asp Arg Lys Lys Leu Tyr Ser Leu Leu Gly
595 600 605
Ile Asp Leu Thr Ala Pro Ser Asn Asn Ser Ser Pro Arg Asp Ser Pro
610 615 620
Cys Lys Glu Asn Lys Ile Lys Lys Arg Lys Gly Glu Glu Ile Thr Arg
625 630 635 640
Glu Ala Lys Lys Ala Arg Lys Val Gly Gly Leu Thr Gly Ser Ser Ser
645 650 655
Asp Asp Ser Gly Ser Glu Ser Asp Ala Ser Asp Asn Glu Glu Ser Asp
660 665 670
Tyr Glu Ser Ser Lys Asn Met Ser Ser Gly Asp Asp Asp Asp Phe Asn
675 680 685
Pro Phe Leu Asp Glu Ser Asn Glu Asp Asp Glu Asn Asp Pro Trp Leu
690 695 700
Ile
705

<210> 187
<211> 595
<212> PRT
<213> Homo sapien

<400> 187
Glu Ser Pro Arg His Arg Gly Glu Gly Gly Gly Glu Trp Gly Pro Gly
1 5 10 15
Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr
20 25 30
Pro Lys Glu Gly Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro
35 40 45
Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys
50 55 60
Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu

```
65                  70                  75                  80
His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu
                85                  90                  95
Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala
            100                 105                 110
Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly
        115                 120                 125
Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser
    130                 135                 140
Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg
145                 150                 155                 160
Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg
                165                 170                 175
Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg Arg
            180                 185                 190
Pro Arg Lys Arg Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu
        195                 200                 205
Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala
    210                 215                 220
Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gly Pro
225                 230                 235                 240
Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly
                245                 250                 255
Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg
            260                 265                 270
Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg
        275                 280                 285
Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala
    290                 295                 300
His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly
305                 310                 315                 320
Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser
                325                 330                 335
Ala Gly Ala Gly Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly
            340                 345                 350
Gly Gly Arg Gly Gly Gly Gly Ala Gly Arg Gly Gly Gly Ala Ala Gly
        355                 360                 365
Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg
    370                 375                 380
Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala
385                 390                 395                 400
Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
                405                 410                 415
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
            420                 425                 430
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
        435                 440                 445
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
    450                 455                 460
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
465                 470                 475                 480
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
                485                 490                 495
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
            500                 505                 510
```

Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
515 520 525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
530 535 540
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
545 550 555 560
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
565 570 575
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
580 585 590
Trp Leu Pro
595

<210> 188
<211> 376
<212> PRT
<213> Homo sapien

<400> 188
Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
1 5 10 15
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
20 25 30
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
35 40 45
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
50 55 60
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
65 70 75 80
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
85 90 95
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
100 105 110
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
115 120 125
Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
130 135 140
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145 150 155 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
165 170 175
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
180 185 190
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
195 200 205
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
210 215 220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
225 230 235 240
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
245 250 255
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
260 265 270
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys
275 280 285

Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
    290   295   300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
305   310   315   320
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
                325   330   335
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
            340   345   350
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
        355   360   365
Asp Leu Ser Ser Ala Arg His Arg
    370   375

<210> 189
<211> 160
<212> PRT
<213> Homo sapien

<400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Leu Gly
 1   5   10   15
Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
            20   25   30
Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr
        35   40   45
Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
    50   55   60
Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
65   70   75   80
Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
                85   90   95
Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
            100   105   110
Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser
        115   120   125
Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His
    130   135   140
Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly
145   150   155   160

<210> 190
<211> 146
<212> PRT
<213> Homo sapien

<400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
 1   5   10   15
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
            20   25   30
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
        35   40   45
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
    50   55   60
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu

65 70 75 80
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
85 90 95
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
100 105 110
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
115 120 125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
130 135 140
Ile Leu
145

<210> 191
<211> 704
<212> PRT
<213> Homo sapien

<400> 191
Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
1 5 10 15
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
20 25 30
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
35 40 45
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
50 55 60
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
65 70 75 80
Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
85 90 95
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
100 105 110
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
115 120 125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
130 135 140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
145 150 155 160
Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val
165 170 175
Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn
180 185 190
Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr
195 200 205
Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile
210 215 220
Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met
225 230 235 240
Met Glu Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn
245 250 255
Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln
260 265 270
Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu
275 280 285
Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys

```
    290                 295                 300
Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp
305                 310                 315                 320
Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln
                325                 330                 335
Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu
            340                 345                 350
Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu
        355                 360                 365
Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr
    370                 375                 380
Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp
385                 390                 395                 400
Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu
                405                 410                 415
Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys
            420                 425                 430
Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu
        435                 440                 445
Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His
    450                 455                 460
Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile
465                 470                 475                 480
Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln
                485                 490                 495
Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu
            500                 505                 510
Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala
        515                 520                 525
Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu
    530                 535                 540
Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu
545                 550                 555                 560
Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
                565                 570                 575
Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys
            580                 585                 590
Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
        595                 600                 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
    610                 615                 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625                 630                 635                 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
                645                 650                 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
            660                 665                 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
        675                 680                 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
    690                 695                 700
```

```
<210> 192
<211> 331
<212> PRT
```

<213> Homo sapien

<400> 192

Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
1 5 10 15
Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val
20 25 30
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
35 40 45
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
50 55 60
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
65 70 75 80
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
85 90 95
Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
100 105 110
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
115 120 125
Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
130 135 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145 150 155 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
165 170 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
180 185 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
195 200 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
210 215 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225 230 235 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
245 250 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
260 265 270
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
275 280 285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
290 295 300
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
305 310 315 320
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
325 330

<210> 193
<211> 475
<212> PRT
<213> Homo sapien

<400> 193

Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu
1 5 10 15
Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser

```
            20                      25                      30
Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn
        35                      40                      45
Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp
    50                      55                      60
Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Glu Gly Asp Thr Ser Leu
65                      70                      75                      80
Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His
                85                      90                      95
Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln
            100                     105                     110
Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg
        115                     120                     125
Pro Val Val Ser Pro Ala Asn Gly Val Glu Gly Val Arg Val Asp Gln
    130                     135                     140
Asp Asp Asp Gln Asp Ser Ser Ser Leu Lys Leu Ser Gln Asn Ile Ala
145                     150                     155                     160
Val Gln Thr Asp Phe Lys Thr Ala Asp Ser Glu Val Asn Thr Asp Gln
                165                     170                     175
Asp Ile Glu Lys Asn Leu Asp Lys Met Met Thr Glu Arg Thr Leu Leu
            180                     185                     190
Lys Glu Arg Tyr Gln Glu Val Leu Asp Lys Gln Arg Gln Val Glu Asn
        195                     200                     205
Gln Leu Gln Val Gln Leu Lys Gln Leu Gln Gln Arg Arg Glu Glu Glu
    210                     215                     220
Met Lys Asn His Gln Glu Ile Leu Lys Ala Ile Gln Asp Val Thr Ile
225                     230                     235                     240
Lys Arg Glu Glu Thr Lys Lys Lys Ile Glu Lys Glu Lys Lys Glu Phe
                245                     250                     255
Leu Gln Lys Glu Gln Asp Leu Lys Ala Glu Ile Glu Lys Leu Cys Glu
            260                     265                     270
Lys Gly Arg Arg Glu Val Trp Glu Met Glu Leu Asp Arg Leu Lys Asn
        275                     280                     285
Gln Asp Gly Glu Ile Asn Arg Asn Ile Met Glu Glu Thr Glu Arg Ala
    290                     295                     300
Trp Lys Ala Glu Ile Leu Ser Leu Glu Ser Arg Lys Glu Leu Leu Val
305                     310                     315                     320
Leu Lys Leu Glu Glu Ala Glu Lys Glu Ala Glu Leu His Leu Thr Tyr
                325                     330                     335
Leu Lys Ser Thr Pro Pro Thr Leu Glu Thr Val Arg Ser Lys Gln Glu
            340                     345                     350
Trp Glu Thr Arg Leu Asn Gly Val Arg Ile Met Lys Lys Asn Val Arg
        355                     360                     365
Asp Gln Phe Asn Ser His Ile Gln Leu Val Arg Asn Gly Ala Lys Leu
    370                     375                     380
Ser Ser Leu Pro Gln Ile Pro Thr Pro Thr Leu Pro Pro Pro Pro Ser
385                     390                     395                     400
Glu Thr Asp Phe Met Leu Gln Val Phe Gln Pro Ser Pro Ser Leu Ala
                405                     410                     415
Pro Arg Met Pro Phe Ser Ile Gly Gln Val Thr Met Pro Met Val Met
            420                     425                     430
Pro Ser Ala Asp Pro Arg Ser Leu Ser Phe Pro Ile Leu Asn Pro Ala
        435                     440                     445
Leu Ser Gln Pro Ser Gln Pro Ser Ser Pro Leu Pro Gly Ser His Gly
    450                     455                     460
```

Arg Asn Ser Pro Gly Leu Gly Ser Leu Val Ser
465 470 475

<210> 194
<211> 241
<212> PRT
<213> Homo sapien

<400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
1 5 10 15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
20 25 30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
35 40 45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
50 55 60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65 70 75 80
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
85 90 95
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
100 105 110
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
115 120 125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Ala Gly Leu Lys Glu
130 135 140
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
145 150 155 160
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
165 170 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
180 185 190
Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu
195 200 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
210 215 220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
225 230 235 240
Leu

<210> 195
<211> 138
<212> PRT
<213> Homo sapien

<400> 195
Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu
1 5 10 15
Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu
20 25 30
Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu
35 40 45
Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys

```
    50                  55                  60
Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu
65                  70                  75                  80
Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu
                85                  90                  95
Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln
            100                 105                 110
Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
        115                 120                 125
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
    130                 135

<210> 196
<211> 102
<212> PRT
<213> Homo sapien

<400> 196
Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr
 1               5                  10                  15
Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala
            20                  25                  30
Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys
        35                  40                  45
Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly
    50                  55                  60
Val Gly Thr Lys Ile Ala Glu Lys Ile Asp Glu Phe Leu Ala Thr Gly
65                  70                  75                  80
Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser
                85                  90                  95
Ile Asn Phe Leu Thr Arg
            100

<210> 197
<211> 138
<212> PRT
<213> Homo sapien

<400> 197
Glu Ala Asn Glu Val Thr Asp Ser Ala Tyr Met Gly Ser Glu Ser Thr
 1               5                  10                  15
Tyr Ser Glu Cys Glu Thr Phe Thr Asp Glu Asp Thr Ser Thr Leu Val
            20                  25                  30
His Pro Glu Leu Gln Pro Glu Gly Asp Ala Asp Ser Ala Gly Gly Ser
        35                  40                  45
Ala Val Pro Ser Glu Cys Leu Asp Ala Met Glu Glu Pro Asp His Gly
    50                  55                  60
Ala Leu Leu Leu Leu Pro Gly Arg Pro His Pro His Gly Gln Ser Val
65                  70                  75                  80
Ile Thr Val Ile Gly Gly Glu Glu His Phe Glu Asp Tyr Gly Glu Gly
                85                  90                  95
Ser Glu Ala Glu Leu Ser Pro Glu Thr Leu Cys Asn Gly Gln Leu Gly
            100                 105                 110
Cys Ser Asp Pro Ala Phe Leu Thr Pro Ser Pro Thr Lys Arg Leu Ser
        115                 120                 125
```

```
Ser Lys Lys Val Ala Arg Tyr Leu His Gln
    130                 135

      <210> 198
      <211> 100
      <212> PRT
      <213> Homo sapien

      <400> 198
Met Gly Asp Val Lys Asn Phe Leu Tyr Ala Trp Cys Gly Lys Arg Lys
 1               5                  10                  15
Met Thr Pro Ser Tyr Glu Ile Arg Ala Val Gly Asn Lys Asn Arg Gln
            20                  25                  30
Lys Phe Met Cys Glu Val Gln Val Glu Gly Tyr Asn Tyr Thr Gly Met
        35                  40                  45
Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp
    50                  55                  60
Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val
65                  70                  75                  80
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
                85                  90                  95
Thr Thr Ala Asn
            100

      <210> 199
      <211> 127
      <212> PRT
      <213> Homo sapien

      <400> 199
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
 1               5                  10                  15
Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
            20                  25                  30
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
        35                  40                  45
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
    50                  55                  60
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
65                  70                  75                  80
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
                85                  90                  95
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
            100                 105                 110
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
        115                 120                 125

      <210> 200
      <211> 90
      <212> PRT
      <213> Homo sapien

      <400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
 1               5                  10                  15
```

His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
            20   25   30
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
        35   40   45
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
    50   55   60
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
65   70   75   80
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
                85   90

<210> 201
<211> 120
<212> PRT
<213> Homo sapien

<400> 201
Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala
 1   5   10   15
Ser Ser Thr Pro Leu Ser Pro Thr Arg Ile Thr Arg Leu Gln Glu Lys
            20   25   30
Glu Asp Leu Gln Glu Leu Asn Asp Arg Leu Ala Val Tyr Ile Asp Arg
        35   40   45
Val Arg Ser Leu Glu Thr Glu Asn Ala Gly Leu Arg Leu Arg Ile Thr
    50   55   60
Glu Ser Glu Glu Val Val Ser Arg Glu Val Ser Gly Ile Lys Ala Ala
65   70   75   80
Tyr Glu Ala Glu Leu Gly Asp Ala Arg Lys Thr Leu Asp Ser Val Ala
                85   90   95
Lys Glu Arg Ala Arg Leu Gln Leu Glu Leu Ser Lys Val Arg Glu Glu
            100   105   110
Phe Lys Glu Leu Lys Ala Arg Asn
        115   120

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
 1   5   10   15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
            20   25   30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
        35   40   45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
    50   55   60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65   70   75   80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
                85   90   95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
            100   105   110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala

```
        115                 120                 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
    130                 135                 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala
145                 150                 155                 160
Gly Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val
                165                 170                 175
Gly
```

```
      <210> 203
      <211> 164
      <212> PRT
      <213> Homo sapien

      <400> 203
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
 1               5                  10                  15
Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu
            20                  25                  30
His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val
        35                  40                  45
Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr
    50                  55                  60
Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr
65                  70                  75                  80
Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu
                85                  90                  95
Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr
            100                 105                 110
Phe Tyr Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met
        115                 120                 125
Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser
    130                 135                 140
Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu
145                 150                 155                 160
Pro Arg Lys Pro
```

```
      <210> 204
      <211> 241
      <212> PRT
      <213> Homo sapien

      <400> 204
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1               5                  10                  15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
            20                  25                  30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
        35                  40                  45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
    50                  55                  60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65                  70                  75                  80
```

```
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
                85                  90                  95
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
            100                 105                 110
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
        115                 120                 125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Asp Gly Leu Lys Glu
    130                 135                 140
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
145                 150                 155                 160
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
                165                 170                 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
            180                 185                 190
Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu
        195                 200                 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
    210                 215                 220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
225                 230                 235                 240
Leu
```

```
<210> 205
<211> 160
<212> PRT
<213> Homo sapien

<400> 205
Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu
 1               5                  10                  15
Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp
            20                  25                  30
Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys
        35                  40                  45
Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu
    50                  55                  60
Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe
65                  70                  75                  80
Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser
                85                  90                  95
Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
            100                 105                 110
Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp
        115                 120                 125
Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His
    130                 135                 140
Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu
145                 150                 155                 160

<210> 206
<211> 197
<212> PRT
<213> Homo sapien
```

```
        <400> 206
Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr
 1               5                  10                  15
Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser
            20                  25                  30
Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro
        35                  40                  45
Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly
    50                  55                  60
Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His
65                  70                  75                  80
Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp
                85                  90                  95
Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu
            100                 105                 110
Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu
        115                 120                 125
Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu
    130                 135                 140
Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro
145                 150                 155                 160
Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met
                165                 170                 175
Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu
            180                 185                 190
His His Thr Glu Gly
        195

        <210> 207
        <211> 175
        <212> PRT
        <213> Homo sapien

        <400> 207
Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg
 1               5                  10                  15
Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr
            20                  25                  30
Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu
        35                  40                  45
Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly
    50                  55                  60
Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu
65                  70                  75                  80
Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Leu Glu Ala
                85                  90                  95
Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu
            100                 105                 110
Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His
        115                 120                 125
Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro
    130                 135                 140
Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu
145                 150                 155                 160
Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro
```

165 170 175

<210> 208
<211> 177
<212> PRT
<213> Homo sapien

<400> 208
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
1 5 10 15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
20 25 30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
35 40 45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
50 55 60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65 70 75 80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
85 90 95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
100 105 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
115 120 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
130 135 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val
145 150 155 160
Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Gly Pro Gly Met
165 170 175
Ile

<210> 209
<211> 196
<212> PRT
<213> Homo sapien

<400> 209
Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
1 5 10 15
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
20 25 30
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
35 40 45
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
50 55 60
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
65 70 75 80
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
85 90 95
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
100 105 110
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
115 120 125

Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
130 135 140
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
145 150 155 160
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
165 170 175
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Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val Thr Gln
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Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp Leu Val
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Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
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50 55 60
Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg
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Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu
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35 40 45
Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val
50 55 60
Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys
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Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
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Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
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Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
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Thr Tyr Val Thr
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Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly Gly Leu Thr Pro Pro
50 55 60
Lys Ser Glu Asp Lys Val Ser Glu Asn Gly Gly Leu Arg Phe Pro Arg
65 70 75 80
Asn Thr Glu Arg Pro Pro Glu Thr Gly Pro Trp Arg Ala Pro Gly Pro
85 90 95
Trp Glu Lys Thr Pro Glu Ser Trp Gly Pro Ala Pro Thr Ile Gly Glu
100 105 110
Pro Ala Pro Glu Thr Ser Leu Glu Arg Ala Pro Ala Pro Ser Ala Val
115 120 125
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130 135 140
Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro
145 150 155 160
Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu
165 170 175
Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly
180 185 190
Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
195 200 205
Arg Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
210 215 220
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
225 230 235 240
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
245 250 255
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
260 265 270
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
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290 295 300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
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                    485                     490                     495
Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
            500                     505                     510
Pro Ala Arg Ala Pro Asp Ala Arg Pro Ala Gly Pro Val Glu Asn
        515                     520                     525
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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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09/122,192	23 July 1998 (23.07.98)	US
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09/219,245	22 December 1998 (22.12.98)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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(54) Title: COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

(57) Abstract

Compounds and methods for treating lung cancer are provided. The inventive compounds include polypeptides containing at least a portion of a lung tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of lung cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.

INTERNATIONAL SEARCH REPORT

Inte   ional Application No
PCT/US 99/01642

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 A61K38/17 C07K14/47 C07K16/18 A61K35/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C12Q A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 30389 A (MILLENIUM PHARMACEUTICALS, INC.; SHYJAN A.) 3 October 1996 see page 112 - page 127	1-60
A	WO 96 02552 A (CYTOCLONYL PHARMACEUTICS, INC.; TORCZYNSKI R. ET AL.) 1 February 1996 see the whole document	1-60
A	YOU L ET AL.: "Identification of early growth response gene-1 (Egr-1) as a phorbol myristate-induced gene in lung cancer cells by differential mRNA display" AM. J. RESPIR. CELL MOL. BIOL., vol. 17, no. 5, November 1997, pages 617-624, XP002106654 see page 618, left-hand column, paragraph 3	1,2,4-7

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 1999	22.10.1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	CUPIDO, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEN S-L ET AL: "Isolation and characterizaton of a novel gene expressed in multiple cancers" ONCOGENE, vol. 12, no. 4, 15 February 1996, pages 741-751, XP002106655 see page 741, right-hand column, last paragraph - page 743	1,2,4-7

INTERNATIONAL SEARCH REPORT	..ɹrnational application No. PCT/US 99/01642

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 16, 17, 24-26, 32, 33, 48-53 and 56-58 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see FURTHER INFORMATION sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see FURTHER INFORMATION sheet, subject 1.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1,2,4-12,16-25 and 27-60 (all partly and as far as applicable):

Polynucleotides comprising the sequence provided in SEQ ID NO:1, their corresponding complement sequences, variants thereof, polypeptides, vectors, pharmaceutical compositions, pharmaceutical compositions for the treatment of lung cancer, vaccines, applications thereof, fusion proteins, diagnostics, monoclonal antibodies and T cells or antigen presenting cells incubated in the presence of said polynucleotides or polypeptides.

Inventions 2-128: Claims 1-60 (all partly and as far as applicable):

Idem as invention 1 but limited to each of the DNA sequences as in SEQ ID NO: 2-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120, 126-181 and as far as applicable.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/01642

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9630389 A	03-10-1996	US 5633161 A	27-05-1997
		AU 708746 B	12-08-1999
		AU 5437896 A	16-10-1996
		CA 2216717 A	03-10-1996
		EP 0817792 A	14-01-1998
		US 5674739 A	07-10-1997
WO 9602552 A	01-02-1996	US 5589579 A	31-12-1996
		AU 700915 B	14-01-1999
		AU 3359295 A	16-02-1996
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		EP 0804451 A	05-11-1997
		JP 10503087 T	24-03-1998
		US 5773579 A	30-06-1998